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THE ROLE OF SYMPATHECTOMY IN THE TREATMENT OF IMMERSION FOOT AND FROSTBITE*

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THE term "frostbite" designates the lesions produced by exposure to cold. Short exposure to extremely low temperatures or longer exposure to moderately low temperatures results in similar conditions, although damage appears to be more localized when caused by low-temperature exposures of short duration.[1] During World War II many cases have resulted from prolonged soaking of the feet in cold water, hence the term "immersion foot." In this connection White[2] draws a distinction between the lesions of immersion foot and those caused by prolonged exposure in southern latitudes coupled with nutritional deficiencies. Many patients with frostbite or immersion foot have late sequelae and present problems of treatment, disability evaluation and rehabilitation. With regard to treatment, the question concerning the value of sympathectomy arises.[3]

PATHOLOGY

Histologic changes in human tissue due to cold have been described.[4–6] In the acute phase there is damage to the endothelium of the smaller vessels and extravasation of fluid. Some workers have demonstrated degenerative changes in small nerve fibers.[7] Tissue necrosis occurs if exposure has been severe. If infection supervenes, its characteristic changes are added to the picture. The skin in any event usually shows more or less superficial areas of necrosis, but if infection can be avoided the lesions have a tendency to heal better than would be expected from the clinical findings. The healing process is characterized by an abundance of fibrosis involving all the tissues of the hand or foot,[5, 8] a change that apparently accounts for the late symptoms.

THE ACUTE PHASE

The clinical picture of the acute phase is fairly characteristic. During exposure the extremities become numb and painless. No covering except hip boots or a full rubber suit prevents immersion foot, and even with this protection frostbite may be sustained in Arctic waters. Constricting bands that slow circulation are said to increase the severity of the lesions. Application of grease to the feet gives only slight protection during exposure.

When the feet begin to warm after rescue, they lose their pallor, and redness, edema and ecchymosis appear. Pain is prominent during the early recovery period and in higher environmental temperatures is severe. It is inadvisable to warm the feet suddenly after exposure, and the best first aid is exposure of the feet in a cool compartment.

Within a day or two the changes become fully developed and the extent of injury may be estimated.

Brownrigg[9] divides cases of immersion foot or frostbite into first-, second- and third-degree types. The first-degree type represents a minimal lesion. There is edema of the foot and sometimes of the ankle and leg, with ecchymosis, hyperemia and bleb formation. There is considerable pain, but the skin may show diminished sensation as high as the knees. The course is relatively benign unless infection develops. Swelling, hyperemia and pain gradually subside, and cutaneous sensitivity in the leg and ankle regresses. Superficial plaques of dry, gangrenous skin may remain on the tips of the toes or on the foot. These fall away, leaving pink new skin. With proper treatment many first-degree cases heal without any residual disability in about six weeks. Approximately 25 per cent of such patients have bothersome complaints of a neuritic or vasospastic nature.

In second-degree cases, all the lesions noted in the first-degree type are present, together with death of tissue in the distal parts of the extremity, involving both the skin and the subcutaneous tissues. Circumscribed gangrene of the toes is frequent. Occasionally the entire distal portion of the foot is affected. This degree of injury heals as does the first-degree type in so far as the acute manifestations are concerned. Isolated areas of gangrene, either dry or infected, remain, necessitating amputa-

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tion of one or more toes. If chronic ulceration of a toe develops, the distal portion of the digit must be amputated, although conservative treatment is in order. The acute phase may be said to be complete when all ulcers or gangrenous areas have been cured, by amputation or otherwise, which requires about three months. Approximately 75 per cent of these patients have annoying complaints of a neuritic or vasospastic nature in addition to any disability that may be caused by the loss of toes

Third-degree immersion foot or frostbite includes the cases that develop gangrene in the deeper tissues proximal to the toes and those in which there is widespread damage to the skin and deeper structures. It includes all the severest cases, such as those with complete gangrene of the foot. Secondary infection is the rule, so that toxic systemic reaction is almost invariably present. Amputation above the ankle is usually required. It must be noted, however, that conservatism is indicated both concerning the time and the selection of the level of amputation. This has been emphasized in a recent report by Lesser.[8] Because amputations are obligatory, late neurologic and vasospastic complications are absent; disability results from amputation alone.

Treatment

The purposes of early treatment are to prevent further damage to tissues in a precarious metabolic state, to relieve pain and to protect the patient as far as possible from toxemia.

Cooling of the parts relieves pain and possibly aids tissue survival through lowering metabolic requirements so that impaired circulation is more nearly adequate. The patient is placed at bed rest as soon as possible after rescue, and the affected parts are protected from trauma by a cradle. Active cooling may then be employed. Two convenient methods are recommended.[3] If the local manifestations are not severe, the member may be swathed in thick bandages and covered with several ice bags. If open lesions or great swelling and discoloration are present, the patient is more comfortable when cooling is carried out by means of a fan at the lower end of a cradle. Sterile water or saline solution may be sprayed over the feet from time to time. The temperature of the skin should be between 75 and 85°F.

If there is evidence of pre-existing dermatophytosis, daily soaks in cool potassium permanganate solution should be employed, other factors permitting. Routine administration of sulfonamide or penicillin seems justified to prevent or combat infection. Inspection for evidence of thrombophlebitis should be made twice daily and appropriate measures instituted early.

If the lesion is third degree, infection and tissue damage progress in spite of treatment. When it becomes obvious that the tissues will not heal or when the general condition demands it, amputation should be performed. Refrigeration anesthesia with amputation near the affected level is advisable; the simplest operation is employed and is followed by skin traction. If the patient is received in poor general condition owing to infection and gangrene of a foot, a tourniquet should be applied near the infected site and the lost tissue should be refrigerated until the general condition is improved.

The lesions of frostbite produced without the wetting factor may be the same as those of immersion foot, particularly when there has been prolonged exposure to cold without opportunity to change the socks. Trench foot, a closely related lesion, sometimes resembles dry frostbite and sometimes immersion foot, depending on the amount of wetting.[8, 10] Ordinary civilian-type frostbite tends to be less diffuse. As was mentioned previously, high-altitude frostbite also seems to produce more localized severe lesions. In my experience, the late sequelae described below have been less prominent in civilian-type lesions. When present they tend to be localized to one or two digits and may be cured by amputation of the distal part of the digit. Otherwise, the clinical course and treatment of trench foot and localized frostbite are similar to those of immersion foot.

Late Manifestations

The late manifestations of immersion foot or frostbite fall into three principal groups: disturbances of cutaneous sensation, inadequate circulation and pain on use.

Disturbances of Cutaneous Sensation

Disturbances of cutaneous sensation are of two kinds, both often being present in the same patient. In all but the mildest cases there is some residual anesthesia or hypesthesia of the skin. As was noted, this may extend to the knee or above in the early stage, but it spontaneously recedes, leaving distal areas of the foot affected. In the chronic state it is usually confined to the plantar surface in the region of the ball of the foot. It may range from complete insensibility to all modalities to dissociation of touch from pain and temperature sense. This symptom tends to run a prolonged course, but makes further spontaneous improvement from the third to the twelfth month. In some patients the dorsal surfaces of the toes remain insensitive for years. Anesthesia of the skin does not, however, seem to constitute a source of annoyance or disability to the average patient.

The second type of disturbance of sensation is hyperesthesia. It may be found in zones adjacent, and usually proximal, to anesthetic areas, and in some first-degree cases is the only evidence of nerve dysfunction. It consists of hyperirritability to ordinary stimuli. The plantar reflex is exaggerated,

and the patient is annoyed by the weight of bedclothes or by walking. The reactions to the varying disability that this symptom creates are mixed. To some patients it is disagreeable, especially when walking; others scarcely notice it except when trying to sleep; still others know that it is present but are not disturbed by it. Although these sensations may be painful, they should be clearly differentiated from the pain described below.

In old, untreated cases of immersion foot, trophic ulcers — so-called "perforating ulcers" — may appear. They are usually precipitated by some local trauma, such as a fracture, but tend to persist after the acute injury has healed. The site is in hyperkeratotic skin of the sole. These lesions are resistant to treatment. They may be in some way associated with persistent disturbance of cutaneous sensation.

Inadequate Circulation

Inadequate circulation as a sequel of immersion foot or frostbite varies from patient to patient, being absent, transient or barely perceptible in some cases and quite prominent in others. The factors influencing its incidence and severity are obscure. It is not necessarily connected with length of exposure, and may be associated with inherent sensitivity of the vasomotor apparatus. Hyperhidrosis is a frequent symptom. At varying periods during the day, particularly in the early morning, the feet are cold, wet and pallid, and beads of perspiration stand out across the volar surface. Attacks of pallid or blue cyanosis with mottling of the skin may occur on exposure to cold. Following such a period, there is sometimes mild hyperemia. These symptoms are not associated with pain at rest, but are unpleasant and annoying. Quantitative studies of extremity circulation in old cases of untreated immersion foot show diminished flow when compared with sympathectomized extremities in the same patients,[11] both extremities originally showing almost identical effects of exposure.[12]

A less frequent symptom of circulatory disturbance is intermittent claudication. It is similar to the corresponding symptom seen in arteriosclerosis, with the exception that it tends to regress spontaneously. Other changes often noted in connection with vasospastic diseases sometimes occur in immersion foot twelve to eighteen months after injury. In an appreciable number of patients the skin of one or more digits becomes atrophic, thin, red and glistening. It is less pliable than normal; fissures and cracks may occur and lead to late ulcerations, not necessarily on the tips of the digits but often in creases about the joints. If the fingers have been affected, contractures and a thin atrophic digit may result, requiring amputation long after the acute stage of the disease has passed.

Intolerance to cold is associated with circulatory changes following frostbite or immersion foot. In untreated cases, cold brings on numbness and tingling. This, together with decrease in agility of the part, especially in the hand, constitutes a disability.

Pain on Use

Pain in the feet on walking in immersion foot and to a lesser extent pain on use of the hands in frostbite — not necessarily associated with cold — is the principal disabling factor. Long after cutaneous sensation has returned to normal and circulatory disturbances have been relieved, pain may persist. This type of pain is to be differentiated from the various painful sensations described above that may arise in connection with other sequelae. It is dull and aching and is deep-seated, seeming to the patient to be situated in the bones and joints. It is brought on by weight-bearing or work and is relieved by rest. There is associated stiffness of the various joints and loss of normal pliability of the structures. A peculiar waddling gait results. This symptom is probably related to the increased fibrosis that follows exposure to cold.[5] In the hand it is represented by a tendency to tire quickly, but is much less frequently seen there.

It should be noted that the victims of immersion foot in particular have associated neuropsychiatric disturbances, which are not, however, related to exposure to cold *per se*. These vary from acute mild episodes of nervousness and irritability to chronic and severer personality disorders. Neuropsychiatric symptoms may overshadow the local organic lesions and render rehabilitation difficult. When these symptoms are present, treatment should of course be primarily directed toward this condition, but local measures need not be neglected.

Sympathectomy

The role of sympathectomy in the treatment of acute immersion foot or frostbite is debatable. In civilian frostbite involving only one or two digits, sympathetic block with Metycaine Hydrochloride seems to hasten healing and to have no ill effect. In more diffuse lesions resulting from exposure to dry cold, repeated sympathetic blocks apparently hasten healing. This is illustrated by the following cases.

Three merchant seamen were cast adrift for three days on the after half of a ship without heating and with few shelter facilities. The air temperature probably varied from 10 to 30°F. The factor of wetting was not prominent during this exposure. When the men were admitted to the hospital, the lesions comprised first-degree frostbite, with edema, ecchymosis and moderate discoloration of the hands. There were blisters at the tips of several digits in each patient. The patients were treated with repeated sympathetic blocks every third or fourth day for three to five treatments each. Dry plaques

separated from the tips of the fingers, leaving new pink, healthy skin beneath by the end of ten to fourteen days. No painful or vasospastic sequelae had developed at the end of six months. One patient was subsequently subjected to prolonged immersion after the second exposure this finger contracted, became atrophic and useless and had to be amputated.

I have not employed sympathetic block or ganglionectomy in acute stages of immersion foot. As

TABLE 1. *Summary of Data on Patients with Immersion Foot.**

Case No.	Nature of Exposure	Degree	Duration of Symptoms on Admission	Symptoms	Treatment	Result
1	8 days in open dory off Grand Banks (2/40)	2nd	Immediate	Hyperemia; acute pain; ulceration of digits.	Physiotherapy†	Returned to work after year; had some deep pain.
2	4 days on raft in Arctic waters (1/41)	3rd	1 mo.	Gangrene of hands and feet	Amputation of hands and feet	
3	3 days on raft above Arctic Circle	3rd (hands and feet); 2nd (knees)	6 mo.	Gangrene of hands and feet; ulcerations over knees.	Amputation of feet and fingers; procaine lumbar sympathetic blocks.	Knee lesions healed quickly.
4	11½ days in boat in North Atlantic (12/42)	2nd	1mo.	Anesthesia+; deep pain in ankles and feet++++.	Alcohol lumbar sympathetic block	Anesthesia relieved; pain unrelieved; spontaneous improvement after 14 mo.
5	1½ hr. on driftwood in North Atlantic (2/42)	1st	5 mo.	Only right foot affected; hyperesthesia+; hyperhidrosis+; cyanotic attacks++; pain+.	Sympathectomy (right)	Apparently relieved of all symptoms; returned to sea duty.
6	16 days in open boat in Arctic waters (12/42)	2nd	2 mo.	Anesthesia ++++; hyperesthesia +++; hyperhidrosis and cold intolerance ++; deep pain ++++.	Physiotherapy	Picture unchanged 6 mo. after treatment
7	4 days in boat in North Atlantic (1/43)	2nd	4 mo.	Anesthesia++; hyperesthesia++; cyanotic attacks++; pain++++.	Alcohol lumbar sympathetic blocks	Relieved of all symptoms except pain; rehabilitated to sedentary task after 1 yr.
8	4 days in boat in North Atlantic (1/43)	2nd	10 mo.	Anesthesia++; hyperesthesia++; hyperhidrosis+++; cyanotic attacks+; pain++++.	Alcohol lumbar sympathetic blocks; sympathectomy.	Relieved of all symptoms except pain; has been disabled 2½ yr.
9	9 days in open boat in North Atlantic (9/42)	2nd	9 mo.	Anesthesia++++; hyperhidrosis++++; intolerance to cold++++; cyanotic attacks+; deep pain++++.	Alcohol lumbar sympathetic blocks; physiotherapy.	Relieved of anesthesia and hyperhidrosis; cold tolerance improved; pain unrelieved; still disabled.
10	12 days in open boat in North Atlantic (6/43)	2nd	6 mo.	Hyperhidrosis++++; deep pain++++.	Physiotherapy	Unimproved after 6 wk.; could not be followed.
11	Several hours in water; 3 days in boat (1/43).	2nd	6 mo.	Anesthesia++; claudication+++; little deep pain.	Sympathectomy	Apparently cured; returned to duty.
12	8 days in open boat in North Atlantic (1/42)	2nd	12 mo.	Anesthesia+; hyperesthesia +++; cyanotic attacks ++; pain++++.	Alcohol lumbar sympathetic blocks.	Relieved of cutaneous symptoms; cyanosis diminished; pain unrelieved.
13	10 days in open boat in North Atlantic (winter of 1917) fractured foot in 1944.	2nd	27 yr.	Anesthesia of soles; trophic ulcer of sole.	Alcohol lumbar sympathetic blocks	Unimproved
14	3 hr. in open boat in North Atlantic (4/44)	1st	6 wk.	Anesthesia++++; deep pain++.	Physiotherapy†	Anesthesia remains on soles of feet; returned to duty 8/44; still has pain.
15	19 days in open boat in Indian Ocean (6/42)	2nd	16 mo.	Intolerance to cold++++; hyperhidrosis++++; deep pain++++.	Alcohol lumbar sympathetic blocks	Improved tolerance to cold; hyperhidrosis relieved; pain unaffected; still disabled.
16	3 hr. on driftwood in North Sea (2/45)	1st	6 wk.	Hyperhidrosis++++; claudication+++.	Alcohol lumbar sympathetic blocks	Apparently cured

*Fifteen patients seen for other conditions gave histories suggesting first-degree immersion foot, with complete recovery within two to six weeks; 7 patients seen for other conditions gave histories suggesting second-degree immersion foot, with complete recovery within six weeks to three months.

†Physiotherapy included cooling, vascular exercises, pavex, infra red rays, and whirlpool as indicated.

in comparatively warm water when his ship was torpedoed in the Pacific. Although he did not develop acute symptoms, within six weeks after the second exposure atrophy and thinning of the skin of a little finger appeared. Within three months White[2] has pointed out, in the acute stage there is evidence of sympathetic-nerve damage — and presumably local sympathetic denervation of the vessels — in the absence of sweating; hyperemia is already present. For treatment of certain of the

sequelae of frostbite or immersion foot, however, sympathetic-nerve block or ganglionectomy appears to be indicated. The clinical features of the cases on which this assumption is based are summarized in the accompanying tables.

It is a singular fact that the disturbances of cutaneous sensitivity are almost invariably removed by sympathectomy. In some patients a temporary sympathetic block not involving the somatic nerves immediately restores cutaneous sensitivity and relieves hyperesthesia. In others there is a return to normal within two or three days after ganglion block by alcohol injection or ganglionectomy, but it should be noted, as already stated, that these symptoms do not usually contribute much to permanent disability. One would hesitate to recommend bilateral ganglionectomy for relief of these symptoms alone. If a block lasting six to eight months can be performed by alcohol injection, it is worth while. Recurrence of sympathetic activity is not associated with return of these symptoms. If the symptoms are particularly distressing and if it is impossible to obtain satisfactory alcohol block, as it is in some cases, sympathectomy is justified.

If persistent and annoying symptoms of circulatory insufficiency resembling vasospasm are present, sympathectomy is helpful. If excessive sweating, Raynaud's phenomenon or intermittent claudication is prominent in the clinical picture, sympathectomy results in marked improvement. Since these symptoms tend to regress spontaneously, the decision to perform sympathectomy may be safely postponed. If thinning of the skin appears within the first three months, sympathectomy should be performed. Otherwise alcohol block may be used for symptomatic relief.

Deep-seated pain, which is often the principal disabling symptom, does not respond to sympathectomy. It appears to be made neither worse nor better. Nor has it, in my experience, been helped by physiotherapy or mechanical appliances for the feet. With time the pain becomes much dulled or the patient becomes accustomed to it, but in some cases it is still so severe after three years that it constitutes a partial disability requiring change of occupation.

Lumbar Sympathectomy and Sympathetic Block

The sympathetic fibers that control the blood vessels of the lower extremities arise in the thoracic and the lumbar and perhaps the sacral segments. Extirpation of the first, second and third lumbar ganglions produces satisfactory sympathetic denervation in the lower extremity. There are interlacing fibers on the anterior surfaces of the bodies of the lumbar vertebras, and a few patients seem to have some crossing of innervation; at least paravertebral blocks of the second and third ganglions of one side — using 2 cc. of 2 per cent procaine to each ganglion, amounts presumably not large enough to diffuse to the opposite side — sometimes produce vasodilator effects on the opposite side. In one patient, however, in whom this effect was constant on several occasions and who later came to bilateral sympathectomy, left-sided sympathectomy produced vasodilatation on the left, without any effects on the right, just as would normally be expected. Excision or accurate alcohol block of the second and third ganglions produces satisfactory vasodila-

TABLE 2. *Summary of Data on Patients with Frostbite.*

CASE NO.	NATURE OF EXPOSURE	DEGREE	DURATION OF SYMPTOMS ON ADMISSION	SYMPTOMS	TREATMENT	RESULT
1	In air temperature of 10°F. for 8 hr. (1938)	3rd (8 fingers)	7 yr.	Stiffness and pain in hands on exposure to cold	Repeated procaine blocks (previous treatment had included amputation and grafts)	No improvement
2	Worked all day standing on ice (1933)	2nd (both feet)	9 yr.	Vasospasm and ulceration of toes; trophic ulcer of sole.	Sympathectomy	Toes healed; trophic ulcer remained.
3	3 days in air temperature of 20–30°F. (1943)	1st (4 fingers)	Immediate	Dry gangrene of fingertips; hyperhidrosis++++.	Repeated procaine blocks	Apparently cured; returned to duty after 6 wk.; re-exposure caused contracture of little finger.
4	3 days in air temperature of 20–30°F. (1943)	1st (2 fingers)	Immediate	Dry gangrene of fingertips; hyperhidrosis++++; hyperesthesia+.	Repeated procaine blocks	Apparently cured in 8 wk.
5	3 days in air temperature of 20–30°F. (1943)	1st (6 fingers)	Immediate	Dry gangrene of fingertips; hyperhidrosis++; anesthesia in fingers++.	Repeated procaine blocks	Apparently cured
6	Shoveled for 3 hr. at temperature of 20°F.	2d (2 fingers)	Immediate	Acute swelling of hand; ulceration of 2 fingers.	Physiotherapy	Amputation of tips of fingers; moderate stiffness of fingers.
7	Worked for 4 hr. on metal parts in air temperature of 30°F. (12/42)	2nd (1 finger)	10 mo.	Intolerance to cold++++; chronic fissures and ulceration; stiffness of distal joint.	Alcohol sympathetic blocks	Ulcer healed but pain remained; end of finger amputated, with cure.

tation in the leg and foot, although in some cases the effect seems to be enhanced by additional block of the first lumbar ganglion. An effort should be made to spare one first lumbar ganglion — at least when doing alcohol block — to avoid disturbances of ejaculatory power. Although it is convenient to speak of the ganglions in respect to the vertebral bodies on which they rest, there is actually variation in the size, shape and number of these structures.

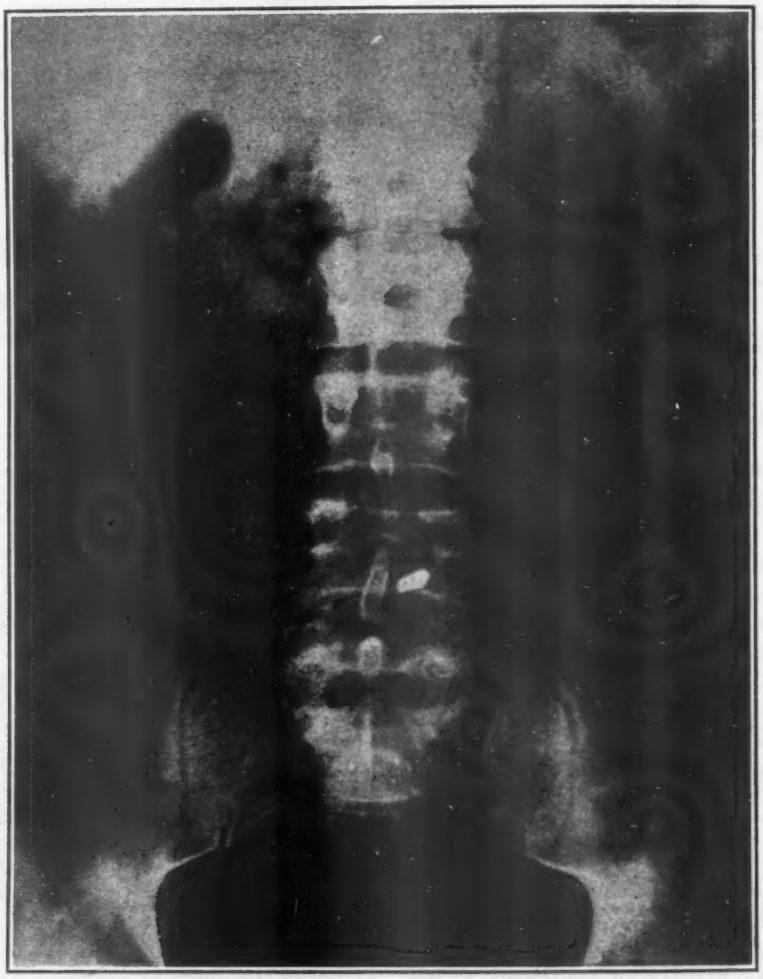

FIGURE 1. *An Aid to Identification of the Lumbar Vertebras for Sympathectomy by the Retroperitoneal Abdominal Approach.*

A metal marker in the umbilicus is projected truly perpendicularly to determine the plane in which the umbilicus lies with reference to the vertebral bodies.

These variations account for the difficulty in some cases of obtaining satisfactory sympathectomy by the blind procedure of alcohol block.

For the average patient, lumbar sympathectomy is simplified by use of the Flothow approach, which has been well described elsewhere.[13] A possible drawback when this method is compared with the lumbar approach, is that it is sometimes difficult to determine accurately the location of the ganglions with respect to a given vertebral body unless an otherwise unnecessary wide dissection is performed. This may in some measure be overcome by use of a preliminary film marking the location of the umbilicus, as shown in Figure 1. For an obese patient or a case in which high spinal anesthesia is not available, the lumbar approach to the sympathetic ganglions is preferable.

For lumbar sympathetic block with alcohol, the patient is placed in the prone position with the spine flexed as well as possible by pillows beneath the abdomen. A preliminary intravenous injection of 11 to 16 mg. of morphine is of value. The spinous processes are counted from the fourth interspace, which lies opposite the iliac crests, and checked by counting from above downward, beginning with the twelfth rib and tracing its course to locate the twelfth thoracic spine. Wheals are made from three to four fingerbreadths lateral to the superior faces of the second and third spinous

processes. A 12.5-cm., 22-gauge, blunt-bevel spinal needle is inserted through the upper wheal and advanced inward and slightly medially to touch the side of the body of the vertebra. If it touches the transverse process instead, it is withdrawn, angled slightly cephalad in addition to its medial angulation and pushed inward until the body of the vertebra is reached. The needle is turned until the bevel faces the body of the vertebra, and the point is slid down the lateral face of the vertebral body until it is felt to pass the anterolateral "corner" of the body. The stylet is removed, and aspiration is done. A second needle is inserted in the same way to the third lumbar ganglion. In this situation the point of the needle may easily enter the vena cava or aorta, but no harm is done if it is slightly withdrawn, to remove the bevel to a more superficial level before injecting. When blocking the ganglions in the lumbar region, there is little fear of making an accidental subarachnoid injection, since the sympathetic trunk and ganglions lie quite deep relative to the somatic nerves and intervertebral foramens. When the point is properly situated, 2 cc. of 2 per cent solution of Metycaine Hydrochloride or procaine is injected through each needle and the effect on the feet is observed.

If this small amount of anesthetic solution quickly produces vasodilatation, accurate location of the needles in or near one or more of the ganglions is indicated. Four cubic centimeters of absolute alcohol is then injected through each needle. This causes an immediate burning pain in the back and may produce painful sensations in the abdomen, but these quickly disappear. Later there is stiffness of the back and dull pain, which should not last through the second day.

For successful treatment, alcohol neuritis of the somatic nerves must be avoided. This occurs when they are speared and alcohol works its way into the nerves or when small amounts of alcohol are injected about them. Even the largest somatic nerves may be injected with alcohol if a sufficient amount is used to produce degeneration, but small amounts serve to irritate them and produce neuritis, which may last for months.

Neuritis is avoided in the following way. First, no attempt should be made to inject the fourth and fifth lumbar ganglions with alcohol. Second, the needles should be inserted in such a way that they will not produce paresthesia down the extremity. This is done by using only a little local anesthetic solution in the muscle beneath the wheal and by injecting none deep to the transverse process until the ganglion has been reached. If any needle in traversing the back toward the body of the vertebra produces pain down the leg or in the hip or genitals, it should be withdrawn and inserted at a different level, usually opposite the center of the spinous process. With regard to paresthesia, insertion of the needle into one of the ganglions produces pain radiating downward to the coccyx, and when this fortunate accident occurs, alcohol may be injected without delay.

The technic of temporary sympathetic block is much less exacting. The needles are inserted in the same manner, but more local anesthetic solution may be used on the way in to make the procedure less painful. When the needles are inserted in approximately the proper location, the area should be flooded with 5 to 10 cc. of 1 per cent solution of Metycaine Hydrochloride or procaine through each needle. This almost always results in sympathetic block. Or temporary block may be done more easily with a caudal or peridural injection.[14, 15]

Thoracic Sympathectomy and Block

It is much more difficult to produce permanent sympathetic denervation in the upper extremity than in the lower. The operation of Smithwick,[16] however, seems to have largely overcome the defects of this procedure. The indications for operative sympathectomy in the upper extremity should be more demanding than for that in the lower, since the operation is somewhat more exacting and difficult than lumbar sympathectomy and at the same time is often less satisfactory.

For diagnostic or therapeutic block of the sympathetic supply to the upper extremity, the first and second thoracic sympathetic ganglions are anesthetized. The patient is placed in the lateral or prone position, and the thoracic and cervical spine is flexed. A wheal is made two fingerbreadths lateral to the spine of the seventh cervical vertebra, and the muscle tissue is anesthetized down to the transverse process of the first thoracic vertebra. From an angle of about 10°, a 22-gauge blunt-bevel spinal or nerve-block needle is inserted through the wheal down to the transverse process of the first thoracic vertebra. The bevel is worked over the transverse process until it drops across its inferior border, and its course is continued inward and slightly medially until the lateral aspect of the body of the vertebra is reached. For diagnostic or temporary therapeutic block, 5 cc. of a 2 per cent solution of procaine should be injected. The same procedure is carried out from a wheal opposite the spinous process of the first thoracic vertebra to block the second thoracic ganglion. Should bone bar the needle's progress 0.5 cc. or less beneath the transverse process, the posterior surface of the body of the vertebra in the region of the intervertebral foramen has been touched, and the needle should be withdrawn and reinserted from a wheal made slightly more lateral. Aspiration should precede injection to avoid subarachnoid injection. Neither procaine nor alcohol should be injected intraneurally into a somatic nerve near the spine, since it is said to be possible to damage the spinal cord by solution forced into it along the nerve.[17]

For alcohol block in the thoracic ganglions, the same procedure is adopted as before, but the preliminary solution superficial to the transverse process is injected sparingly. When the needles seem properly placed in the region of the ganglion on the lateral aspects of the bodies of the vertebras, 2 cc. of a 2 per cent solution of procaine is injected through each needle and the effect is observed. If prompt vasodilatation occurs from such a small amount of procaine, the needle is situated in or very near the desired location. Four cubic centimeters of absolute alcohol is injected through each needle, which is then withdrawn and inserted to the posterior surface of the body of the vertebra near the intervertebral foramen above the ganglion injected. Aspiration with a dry syringe should be done, making sure that no spinal fluid appears. In these positions an additional 1 cc. of absolute alcohol should be injected through each needle to block the first and second thoracic somatic nerves.

The somatic nerves are deliberately blocked in this instance with sufficient alcohol to produce at least partial degeneration. This is done to prevent painful neuritis, since in the thoracic region it is practically impossible to inject the sympathetic ganglions without affecting the intercostal nerves. Although intercostal neuritis is seldom so severe as lumbar plexus neuritis, it is to be avoided. No disturbance of function seems to result from this procedure, despite the fact that the first thoracic nerve contributes to the brachial plexus. Somatic anesthesia thus produced lasts scarcely a month, although a proper sympathetic block lasts for six to eight months.

Additional dangers of thoracic injection are present that are not encountered in the lumbar region. There is always the possibility of spinal anesthesia from injecting into an intervertebral foramen or into an extra long dural sleeve. As was described above, careful aspiration with a dry syringe before injection should serve to prevent this accident. The injection is begun rather closer to the midline than it is in the lumbar region to avoid entering the pleura, since if this is pierced, together with the lung, painful apical pneumothorax may result; but this is not dangerous unless the patient is emphysematous. If the needle is not inserted along the bony landmark, it may go astray and pierce the esophagus, but this does no harm. I have not pierced a large vessel in doing this injection, but it might happen. So long as anesthetic solution is not injected intravascularly, no harm will result.

It should not be concluded from the relative space devoted to alcohol block and ganglionectomy that the former procedure is always the technic of choice for producing sympathetic denervation. Ganglionectomy is the more exact and often the more satisfactory method. It is hoped that the block technics herein described will be of assistance to others in avoiding alcohol neuritis.

Evaluation of Disability

In evaluating disability as a result of frostbite and immersion foot, it should be borne in mind that in first- and second-degree cases the changes may not become static until eighteen months after injury. In third-degree cases the diseased parts are usually amputated, so that earlier evaluation is often possible. In examination of patients of the first two types, particular attention should be paid to the amount of pain in the feet from walking and pain in the hand from working. If a history is spontaneously given of deep-seated aching pain "in the bones," it is usually valid. The amount of disturbance of pliability of the structures should be estimated. The condition of the skin with regard to atrophy should be noted, together with evidences of circulatory insufficiency. Most patients presenting vasospastic signs have not reached the maximum benefit of medical treatment. Circulatory disturbance with the skin already thinning represents a real danger of future contracture or ulceration.

Many patients with first-degree frostbite or immersion foot completely recover. In frostbite of the fingers particularly, the disability may be limited to one finger. About half the patients with second-degree immersion foot showing late sequelae remain disabled for work involving prolonged standing or walking. Many of them cannot work under all weather conditions; patients with frostbite of the fingers usually cannot do manual labor in cold weather, and some, depending on the number of fingers affected and the extent of deep-seated pain, cannot perform skilled manual labor.

The problem of rehabilitation of disabled sufferers from immersion foot or frostbite involves knowledge in many fields, but the medical facts, especially those with reference to pain, stamina and effects of climate, should be scrupulously regarded.

Summary

Careful study of a small group of patients with immersion foot or frostbite indicates that sympathetic denervation produces beneficial effects on certain late symptoms but does not always prevent partial disability. It is probable that similar results can be obtained in cases of trench foot showing similar lesions.

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PENICILLIN IN THE TREATMENT OF TETANUS*

Report of Two Cases

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TETANUS is an extremely serious disease, whose mortality rate remains extremely high in spite of the institution of heroic measures for combating the intoxication and controlling the convulsive seizures that it produces. Treatment of this infection necessitates the careful control of at least five factors if a successful outcome is to be expected. Often, even with the most rigid adherence to these principles, failure results.

Of the greatest importance is the rapid and effective neutralization of absorbed tetanus toxin. If this has already been fixed to nervous tissue, it apparently cannot be inactivated by antitoxin, regardless of how large a quantity is given. The sole effect of the administration of antiserum therefore appears to be the neutralization of toxic material still circulating in the blood stream and the maintenance of an antitoxic level sufficiently high to overcome the effect of any additional tetanospasmin that may be absorbed from the local focus of infection. The antitoxic serum must be administered initially in large amounts and repeated at frequent intervals for several days to a week or more. An adequate procedure is the injection of 50,000 American units intravenously, 50,000 units intramuscularly and 10,000 to 20,000 units subcutaneously around the local wound, if one is present. Ten thousand units should be given every twenty-four hours thereafter until the condition of the patient warrants cessation of antitoxic therapy.

All patients with tetanus have muscle spasm ranging in severity from that involving only the tissue immediately surrounding the site of injury (local tetanus) to that in which severe, generalized tonic convulsions are initiated by the slightest stimulus. A great variety of drugs have been employed to relieve spasm and convulsions, and almost everyone who has treated tetanus has his favorite. Thus, magnesium sulfate, morphine, avertin, paraldehyde, sodium luminal and inhalation anesthesia have all been used. Each of these agents has its proponents, but it appears that any agent is adequate that is capable of exerting a strong anticonvulsive effect with minimal danger from the necessarily large and frequent doses. Any of these sedative drugs must be given in large enough amounts and frequently enough to induce complete and prolonged relaxation. Careful watch must be kept for signs of overdosage.

Many patients with tetanus are unable to take food because of inability to open the mouth owing to spasm of the jaw muscles or because attempts at eating initiate convulsive spasms. For this reason, it is often impossible to maintain a normal state of nutrition by means of the oral route, rendering it essential that adequate calories and vitamins be administered, at first parenterally and then by means of gavage, until the patient can take food by mouth without discomfort. The plasma protein may fall to low levels because of inadequate food intake, and a close check should be kept on it.

Rigid attention must be paid to the fluid and electrolyte balance in tetanus patients, because they cannot take water by mouth and may lose fluid and salts with extreme rapidity as a result of the sweating and fever that accompany the convulsive seizures. Consequently, 5 per cent glucose in water or physiologic sodium chloride solution should be given parenterally in adequate quantities. The

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blood chloride and nonprotein nitrogen levels should be frequently determined.

Since the toxin that is responsible for all the symptoms is formed by *Clostridium tetani*, which has invaded and propagated in an area of injury, it is imperative that this focus of infection be removed to stop the further production and absorption of toxin. At present, the method of accomplishing this is surgical extirpation of the wound with a wide margin of healthy tissue around it and subsequent treatment with an oxidizing agent, such as activated zinc peroxide. This procedure is adopted when a single lesion is present. It may not be practical or even possible in certain cases with multiple lesions in those in which surgical removal of the local lesion would be seriously mutilating and in those in which no localized focus of infection can be discovered.

Penicillin has been shown by Herrell, Nichols and Heilman[1] to be active against *Cl. tetani* in vitro. The administration of this antibiotic agent to patients with tetanus infection and intoxication should therefore be a highly valuable aid to surgical measures, in eliminating whatever bacteria may remain after removal of a single lesion or in eradicating organisms that cannot be reached by surgery. Reports of the use of penicillin in the treatment of tetanus are rare. Buxton and Kurman[2] have described 2 patients with tetanus both of whom recovered after treatment with large doses of penicillin and antitoxin.

The purpose of administering penicillin in the 2 cases described below was to determine the efficacy of the antibiotic substance in eliminating tetanus bacilli from wounds, and to ascertain whether the administration of this agent had a favorable effect on the course of the disease.

Case Reports

Case 1. W. B., a 30-year-old man, was admitted to the hospital with a chief complaint of pain and stiffness of the right jaw of 3 days' duration. The family history was irrelevant. The patient had been rejected by Selective Service because of asthma and bronchitis.

Two weeks prior to entry to the hospital, while repairing a tire on his automobile, the patient received a large, triangular-shaped laceration on the dorsum of the left hand when the car slipped off of the jack. He was seen within a short time by a physician, who, after cleaning and irrigating the wound, dusted sulfanilamide powder into it. During the next 10 days, the injured area was again cleaned and treated with sulfanilamide powder and appeared to be healing well. Seventy-two hours before admission, pain and stiffness of the right jaw, most marked when chewing and absent when not eating, was noted. This persisted but did not increase in severity. Two days after the onset of these symptoms, the patient again consulted his physician. Examination at that time revealed some stiffness of the right jaw but no marked trismus. Since no antitoxin had been given following the hand injury, the possibility of tetanus was considered and the patient was referred to the Haynes Memorial Hospital. There was no history of headache, stiffness of the back or neck or localized spasm of the arm or hand around the wound.

Physical examination on admission revealed a well nourished, well developed man who appeared quite healthy. The temperature was 98.6°F., the pulse 68, and the respirations 18. There was a triangular laceration 8 cm. in its longest diameter, crusted with dried sulfanilamide powder, on the dorsum of the left hand. The skin around the wound appeared normal in color and was not swollen or tender. There was no cervical, axillary, epitrochlear or inguinal lymphadenopathy. Examination of the head was essentially negative, and the neck could be flexed anteriorly and laterally with great ease. The pupils were round and equal, and reacted to light and on accommodation. The extraocular movements were within normal limits. Examination of the eyegrounds revealed no abnormalities. The patient was unable to open the mouth widely because of pain at the angle of the right mandible. Palpation of the masseters revealed no spasm, but there was a point of tenderness 3 cm. anterior to the angle of the right jaw. Examination of the teeth revealed swelling of the gums and tenderness over the lateral side of the lower right 3rd molar. The pharynx could not be well visualized because the mouth could not be opened beyond 2 fingerbreadths. The lungs were clear to percussion and auscultation. The heart was not enlarged, the sounds were of good quality, the rhythm was regular, and no rubs or murmurs could be detected. The aortic second sound was louder than the pulmonic. The blood pressure was 118/70. The abdomen was soft, with no demonstrable tenderness, spasm or hernias. The liver, spleen and kidneys were not palpable. The genitalia were within normal limits. All the muscles were strong, and no evidence of spasm was found. There was no limitation of motion of any of the joints. All the deep and superficial reflexes were present, equal and of normal activity. The cranial nerves were intact. Kernig's and Chvostek's signs were negative. The patient was mentally alert and extremely responsive.

Laboratory examinations on admission revealed no albumin, sugar, ketone or abnormal cellular elements in the urine, which had a specific gravity of 1.018. The hemoglobin was 15 gm. The white-cell count was 10,000, with 70 per cent neutrophils, 26 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils.

Because of the demonstration of localized disease over the 3rd right molar, which might account for the slight trismus and the absence of any other signs of tetanus, it was decided to withhold antitoxin. The history of asthma contributed to this decision, although endermal and conjunctival tests with horse serum gave no reactions.

Ten hours after admission, the patient complained of cramping, generalized abdominal pain, coming on for short periods of time, and a "crushing feeling" over the precordium, radiating straight through to the back. These symptoms were accompanied by a sensation of suffocation. Examination revealed slight stiffness of the back, moderate spasm of the abdominal muscles and the same degree of trismus as had been noted on admission.

Because the development of the abdominal muscle spasm was thought to be due to the action of tetanus toxin, tetanus antitoxin was administered in the following manner: 50,000 units was given intravenously, 50,000 intramuscularly and 10,000 subcutaneously around the wound on the dorsum of the hand. At the same time a regimen of 15,000 units of penicillin every 3 hours and paraldehyde intramuscularly varying in amounts from 20 to 60 cc. a day was instituted. The surgical consultant who excised the hand wound found boardlike rigidity of the abdomen 4 hours after the onset of pain and suggested the possibility of a ruptured viscus, particularly since x-ray examination revealed obliteration of the left psoas shadow. An exploratory laparotomy was therefore performed, but no intra-abdominal disease was found. Postoperatively, Wangensteen suction was maintained for 48 hours. A lumbar puncture carried out prior to operation revealed no abnormality of the spinal fluid. The temperature ranged between 101 and 103°F. for the first 6 postoperative days and then returned to normal.

During the next few days, 10 cc. of paraldehyde was administered intramuscularly every 4 hours, and this maintained the patient at practically continuous rest. Penicillin was continued for 12 days at a rate of 160,000 units a day. The Kernig reaction gradually became positive. Marked spasm of the abdominal and back muscles persisted, accompanied by pain, of which the patient complained bitterly. There was also rigidity of the neck and a moderate degree of trismus. Ten thousand units of tetanus antitoxin were given intramuscularly every 24 hours for 6 days fol-

lowing the administration of the original dose. The muscle spasm gradually relaxed, the pain in the abdomen diminished slowly, and 8 days after admission the patient was sleeping comfortably without sedation and complained very little of muscle spasm anywhere. The wound in the hand healed well without grafting and was completely closed 4 weeks after excision.

On the 19th day, the patient complained of numbness and severe pain in the left lower extremity. Examination showed the entire leg to be swollen and tense; it was mottled purplish gray, and the superficial saphenous vein could be palpated as a firm structure for almost its entire course in the thigh. There was tenderness to palpation in the inguinal region but not over the saphenous vein, and marked calf tenderness on the left. Homans's sign was absent. The arterial pulsations in both legs were within normal limits. At that time the temperature rose to 105°F. and remained between 99 and 100° for the next 8 days, after which it returned to normal for the remainder of the hospital stay. A diagnosis of left femoral and iliac thrombophlebitis with moderate vasospasm was made, and treatment by hot moist packs and papaverine, 30 mg. every 6 hours, was instituted. Severe pain in the left thigh and tenderness of the calf and upper leg persisted for 5 days, after which they diminished. The swelling and tenderness of the leg gradually decreased, but these were still present to a moderate degree when the patient was discharged 43 days after admission.

A gram stain of smears made directly from the wound at the time of admission showed no organisms that could be recognized as the tetanus bacillus. Cultures of the hand made at the same time revealed vegetative and spore forms of *Cl. tetani* in large numbers. Subsequent bacteriologic examination of the wound on the hand was carried out every 12 hours for the first 4 days and every 24 hours thereafter for the next week. Twenty-four hours after treatment with antitoxin, surgery and penicillin had been instituted, the anaerobic organism could not be demonstrated in the wound, and it was not recovered in any of the later cultures.

Laboratory examinations made during the course of the illness revealed urines that were always within normal limits. The white-cell count, which, as previously stated, had been 10,000 on admission, fell to 2000, with 42 per cent neutrophils and 58 per cent lymphocytes, 2 hours after the administration of the tetanus antitoxin. Eight hours later, it had risen to 21,000, with 89 per cent neutrophils, and for the next 3 days it ranged between this level and 34,600. Thereafter it returned to within normal limits until the episode of thrombophlebitis, when it again rose, to 17,650, with 80 per cent neutrophils; it then declined gradually and at the time of discharge was 7750, with a normal differential count. The hemoglobin ranged between 12 and 15 gm. The nonprotein nitrogen varied from 33 to 35 mg per 100 cc. and the serum protein from 5.7 to 6.1 gm., with 3.5 to 3.6 gm. of albumin per 100 cc. The plasma chloride level was 94.3 milliequiv. per liter. An electrocardiogram taken 3 days after admission was within normal limits.

Case 2. R. P., a 4-year-old Negro, was admitted to the Haynes Memorial Hospital with a diagnosis of tetanus. The family and past histories were irrelevant. The illness began 10 days prior to admission, when the patient's mother noticed a cut on his finger. No attention was paid to this, and he got along well until the morning of entry to the hospital, when it was noted that he could not stand up. A physician discovered severe trismus and muscle spasm and sent the patient to the hospital.

On admission, the temperature was 99.4°F., the pulse 84, and the respirations 26. Physical examination revealed a well developed, thin boy who appeared acutely ill. He was in marked opisthotonos, with the back sharply hyperextended and both feet extended in the equinus position. The skin was flushed, and the veins of the head were engorged. Examination of the head was essentially negative. There was marked rigidity of the neck. The pupils were small, round and equal and reacted to light and accommodation. The teeth were clenched tightly, but the patient could open his mouth voluntarily about 1 cm. to permit passage of a glass drinking straw. The lungs were clear to percussion and auscultation. The heart was not enlarged, the sounds were of good quality, there was sinus arrhythmia with a tachycardia, and no murmurs were heard. The pulmonic second sound was greater than the aortic. The blood pressure was 130/84. Examination of the abdomen revealed marked spasm of all the muscles and hyperactive but equal reflexes. The genitalia were within normal limits. All the extremities were in marked spasm and could not be extended or flexed except with great difficulty. On the medial aspect of the left malleolus there was a deep wound 1 cm. in length, covered with purulent exudate. Over the lateral aspect of the right heel there was a ruptured vesicle that did not appear to be infected. The skin over the terminal phalanges of the 2nd, 3rd, 4th and 5th toes of the right foot was lacerated in numerous places, but no signs of infection were present. One third of the nail of the 4th finger of the left hand was easily removed and revealed thin, greenish-yellow, foul-smelling pus; the eponychium was red and swollen.

Immediately after admission the patient was given 40,000 units of tetanus antitoxin intravenously, 30,000 units intramuscularly, 10,000 subcutaneously about the wound on the 4th finger of the left hand and 10,000 units under the skin around the lesion on the medial aspect of the left foot. Sodium luminal (0.13 gm.) was given parenterally as often as required to keep the patient at rest. Physiologic saline solution was administered subcutaneously. Penicillin was given in a dosage of 10,000 units every hour by constant intramuscular drip and continued for 11 days. Shortly after injection of the horse serum the patient had several convulsions, but these were controlled by sodium luminal. A generalized urticarial rash appeared 30 minutes after giving the antitoxin, but disappeared after the administration of 0.25 cc. of a 1:1000 solution of epinephrine given every 15 minutes for 1 hour.

The terminal phalanx of the 4th finger of the left hand was amputated, and the wound on the left ankle was incised and drained. More extensive surgery for removal of all the infected tissue could not be carried out because of the mutilation that would have resulted. Convulsions occurred frequently, even with large doses of sodium luminal and paraldehyde injected rectally as an adjuvant to the barbiturate therapy. Fifteen hundred units of tetanus antitoxin were given every 24 hours for 2 days and then increased to 10,000 units daily for 7 days. On the 3rd day, an attempt to pass a tube through the nose resulted in profuse bleeding from both nostrils and the mouth, and no further attempt was made until the 7th day, when a tube was successfully passed and frequent feeding was instituted. For the first week fluid and electrolyte balances were maintained by the subcutaneous and intravenous administration of glucose, salt and vitamins. On the 5th day, the patient had numerous convulsions, only partially controlled by sodium luminal and paraldehyde. The use of both these drugs was stopped and magnesium sulfate was administered intramuscularly. This agent controlled the convulsions well until the 8th day, when it was discontinued because it was thought to have produced respiratory arrest. The convulsive seizures were easily controlled thereafter with moderate doses of sodium luminal and paraldehyde, administered parenterally.

On the 8th day, there appeared to be some relaxation of the muscles of the jaws. On the 10th, 11th, 12th and 16th days, the patient had sudden severe tonic spasms during which respirations ceased and he became markedly cyanotic for 1 to 1½ minutes. Artificial respiration was extremely difficult because of the boardlike rigidity of the chest and abdominal muscles during these seizures, and breathing was apparently resumed spontaneously. The temperature, which had been only slightly elevated, rose to 105°F. on the 10th day, but fell rapidly so that it was within normal limits within 24 hours; it remained so during the remainder of the hospital stay. After the 16th day, the patient began to improve markedly, gradually required less sedative drugs and lost the muscle spasm. At the end of 3 weeks in the hospital, sedation was no longer necessary, increased muscle tonus had almost completely disappeared, and the patient was taking food by mouth. He was kept in the hospital for another 5 weeks to regain his strength and weight, and 59 days after admission he was discharged to the care of a physiotherapist because of residual weakness and slight difficulty in walking.

During the illness the white-cell count ranged from 10,250 on admission to 24,900 on one occasion, with an average of 16,000; the differential count was always within normal limits. The urine showed no abnormalities on numerous examinations. The hemoglobin varied between 7 and 10.5 gm. The nonprotein nitrogen was 23 mg. per 100 cc. The plasma

protein level was 5.3 gm., with 3.6 gm. of albumin per 100 cc. Gram stains of all the wounds revealed no tetanus bacilli, but these were obtained in culture from the wounds in the hand and foot. Cultures were made every 24 hours, but all were negative after penicillin therapy was instituted.

Discussion

The favorable results obtained in these cases indicate that penicillin is a valuable adjuvant in the treatment of tetanus. The administration of large quantities of antitoxin and careful control of convulsions, as well as the maintenance of a good nutritive state and fluid balance, cannot be replaced by any antibacterial agent, regardless of its potency. Surgical removal of local areas of infection is important, but penicillin is probably a valuable aid in eliminating any organisms that are not removed by such a procedure. In cases of tetanus in which there are multiple lesions not all of which can be removed because of the resultant extensive mutilation, penicillin seems to be strongly indicated. Case 2 is a good example of such a situation. Penicillin appears to be of the greatest value in the cases of tetanus infection in which no localized area of bacterial invasion can be detected or in which it is impossible to eradicate the focus surgically.

Summary and Conclusions

Two cases of severe tetanus are reported in which recovery followed treatment with large amounts of antitoxin, surgical excision of the wounds and administration of large doses of penicillin.

Bacteriologic studies revealed that *Clostridium tetani* could no longer be isolated from the wounds in these patients twenty-four hours after the first administration of penicillin. The already demonstrated antibiotic influence of penicillin on this organism in vitro therefore appears to be confirmed in vivo.

The use of penicillin in tetanus appears to be most valuable in cases in which multiple lesions not all of which can be removed by surgical means are present or in which no focus of infection is detectable. This antibiotic agent is not intended to replace the administration of antitoxin, excision of wounds, adequate sedation and maintenance of a normal state of nutrition and hydration, but appears to be a highly important adjuvant to these other therapeutic measures.

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DIABETIC NEUROPATHY*

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THE frequency of neurologic abnormalities, particularly pain and paresthesias, in patients with diabetes mellitus prompted early observers to attribute the diabetes to a lesion of the nervous system. De Calvi[1] in 1864 was the first to consider that the diabetes might be the cause of the neurologic symptoms. Auché,[2] in a review of the literature published in 1890, stated that in diabetic patients all the nerves except those of the bladder and rectum could be involved. Woltman and Wilder[3] in 1929 found only 42 reports, none of them between 1908 and 1928, of a pathologic examination of the spinal cord and peripheral nerves of diabetic patients. They examined the peripheral nerves of 10 such patients, in 3 of whom the spinal cord was also studied. In the single patient who had neurologic signs sufficient to justify a diagnosis of pseudo-tabes dorsalis, they found only a slight degeneration of the cord but marked changes in the peripheral nerves. They ascribed diabetic neuropathy to arteriosclerotic changes in the vasa nervorum. Wagener, Dry and Wilder,[4] confirming these findings, claimed that the neuritis, like diabetic retinitis, was due to some injury to the small venules and arterioles, but later Wilder[5] admitted that he was not altogether satisfied with this explanation. In 1936, Jordan[6] classified diabetic patients with neurologic symptoms in three groups, — hyperglycemic, circulatory or degenerative, and neuritic, — according to his concept of the probable etiology in each.

Cobb and Coggeshall[7] included diabetes with pellagra, beriberi and cachexia as one of the deficiency and metabolic disorders capable of causing neuritis. Williams and Spies[8] more specifically suggested that a deficiency in vitamin B_1 might be the cause of diabetic neuritis. Root[9] believed that uncontrolled diabetes of long duration has some specific effect on nerve tissue, either by a direct metabolic influence or indirectly by means of a dietary deficiency. He admitted that thiamine may play a role in diabetic neuropathy, but contended that the rate of recovery after vitamin therapy is not always rapid or consistent enough to support the

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belief that the disturbance is due solely to vitamin lack. White,[9] on the other hand, classified diabetic neuritis in children under the heading of deficiencies.

Jolliffe, McLester and Sherman,[10] in discussing the prevalence of various types of nutritional polyneuropathy in diabetic and alcoholic patients, suggested that thiamine deficiency might account wholly or in part for such disorders as characteristic bilateral symmetrical polyneuropathy, combined system disease, Wernicke's syndrome and certain organic reaction psychoses.

Meiklejohn[11] questioned the characterization of thiamine as the so-called "antineuritic vitamin." He pointed out that although thiamine therapy remedied the functional metabolic disturbance of nerve tissue produced by lack of this substance, the exact relation of thiamine to the organic changes of polyneuritis was still unknown.

The early experimental work in the production of polyneuropathy in animals by induced thiamine deficiency was extremely disappointing. Moreover, polyneuropathy could be produced in different species of animals by diets deficient in riboflavin, pyridoxin and panthothenic acid only, and could be cured by the administration of these components of the vitamin B complex.[12] This suggested that various species of animals might react differently to deficiency of the various components of the vitamin B complex.

Street[13] found that a diet deficient in thiamine produced irreversible neurologic changes in dogs. He had maintained the animals on a partially thiamine-deficient diet until signs of peripheral neuritis developed. Large doses of thiamine chloride given during the following month had no therapeutic effect, and histologic examination revealed degeneration of the peripheral nerves, anterior horns and posterior columns of the cord.

Swank and Bessey[14] observed in pigeons, and Leblond and Chaulin–Serviniere[15] in monkeys, that the nature and extent of neurologic changes depended on the degree and duration of the vitamin deficiency. Severe or total deprivation of thiamine caused rapid prostration and death, without neurologic signs or pathologic changes in the nervous system. With partial restriction of thiamine over a considerable period of time, it was possible to produce definite signs and histologic evidence of polyneuropathy.

Needles[16] found no history of deficient intake of thiamine in his patients with diabetic neuropathy. He[17] treated 7 patients with advanced neuropathy with thiamine chloride and observed no objective improvement in 4. He believed that the pathologic changes in these patients were irreversible. On the other hand, Fein, Ralli and Jolliffe[18] administered thiamine by mouth to 9 diabetic patients with symmetrical peripheral polyneuropathy and observed complete recovery in 8 and some improvement in 1. Joslin, Root and Bailey[19] believed that the improvement in these cases was related not only to the thiamine administered but also to simultaneous regulation of the diabetes.

Williams and his co-workers[20, 21] made observations in man similar to those made by others[13–15] in animals. They found that prolonged *partial* restriction of thiamine produced neurologic disturbances such as weakness and paralysis of the thigh muscles and diminished vibratory sensation. The ankle jerks and knee jerks first became hyperactive, later diminished and finally disappeared. Early in the experiment, the subjects developed weakness, anorexia, nausea, epigastric distress and vomiting. Later there appeared marked weight loss, giddiness, apathy, confusion, inactivity and numbness, and tingling in the legs. The response of the neuropathy to thiamine therapy was extremely slow, and in 1 case the knee jerks and ankle jerks were still absent after four months of treatment. Williams concluded that polyneuropathy is a manifestation of advanced rather than of early thiamine deficiency.

Neuropathy in diabetic patients, however, is not the clear-cut syndrome that has been produced in animals and man by diets deficient in vitamins. In my experience it is frequently diffuse and disseminated and often presents a bizarre picture. The predominant manifestations may be of cerebral origin or be related to the spinal cord, or may be the result of changes in the peripheral nerves. Even neurologic syndromes, such as combined system disease or tabes, have been noted. Diabetic neuropathy also may simulate tumors or degenerative diseases of the nervous system or malignancy of the gastrointestinal tract.

In occasional patients the objective manifestations of the neuropathy are extremely marked when the subjective complaints are minimal. In most patients, however, the subjective manifestations of diabetic neuropathy develop first and may be present for a long time before definite neurologic signs can be elicited. In these the diagnosis of hysteria or psychoneurosis has frequently been considered before the true situation has been recognized.

Although diabetic neuropathy may involve any part of the nervous system, there is nevertheless a definite predilection for the peripheral nerves. This is of diagnostic significance in patients in whom other types of neurologic abnormality predominate, since the simultaneous existence of a peripheral neuritis makes the diagnosis of diabetic neuropathy likelier. It must be remembered, however, that in the diabetic patient the peripheral neuritis may be asymmetrical.[22]

Also of diagnostic value is the fact that the spinal-fluid protein may be elevated in patients with minimal objective evidence of neuropathy. In other diabetic patients with signs of advanced neuropathy, however, the spinal-fluid protein is normal or only slightly elevated. A tabetic type of gold-sol curve has occasionally been observed.

An occasional finding in diabetic patients in the absence of definite neurologic signs is an unsteady gait or a tendency to fall. This is usually due to muscular weakness, which, although not severe at rest, may on walking progress to the point of bringing the patient to a halt or even causing him to fall. A related phenomenon is pain in the calf of the leg of the intermittent claudication type, which, although ordinarily ascribed to peripheral sclerosis, is not infrequently observed in patients with other signs of diabetic neuropathy. This manifestation of thiamine deficiency has been observed in beriberi and has been attributed to impaired carbohydrate metabolism and the resultant abnormal accumulation of metabolites in muscles.[23] Atony of the bladder with urinary retention, sometimes seen in the diabetic patient in the absence of neurologic signs,[24] may have the same pathogenesis.

Occasionally, diabetic neuropathy is also accompanied by isolated muscle atrophies that may be mistakenly attributed to the local effect of injected insulin. Such atrophies have, however, been observed in muscles remote from the site of injection[6] and even in patients who are not taking insulin.

I consider diabetic neuropathy a manifestation of a diffuse disturbance that may involve the entire nervous system, thus producing a neuropathy of disseminated distribution. Manifestations of vitamin B complex deficiency are frequently associated with the neuropathy and improve simultaneously with the neurologic disorder on vitamin therapy. A few illustrative cases will serve to demonstrate these points.

Case Reports

Case 1. R. M. (B. I. H. 43220), a 65-year-old woman, was first seen in September, 1938. Diabetes had been discovered 3 months previously and had been easily controlled, at first by diet and later by the addition of small doses of insulin. Despite control of glycosuria, there was generalized pruritus, furunculosis and carbuncles. The patient became progressively confused and resistive and developed paranoid trends.

Examination showed a red, beefy tongue and cheilosis. The gait was ataxic, and there was a positive Romberg sign. There was impairment of vibration and position sense in both legs. The left knee jerk was absent, and both ankle jerks were diminished. There was a Babinski sign on the left.

The patient was given a high-calorie diet, yeast tablets by mouth and daily injections of 10 mg. of thiamine chloride. After 3 months of this regimen the skin lesions had completely cleared, but the knee jerks and ankle jerks had disappeared and the mental state remained unchanged. There developed in addition a short episode of weakness of the internal rectus and right facial palsy. After 4 months of vitamin therapy the mental state improved. Nevertheless, parenteral thiamine and yeast were continued, and 15 months later the patient was mentally completely normal. At that time the knee jerks and ankle jerks were still absent. The tongue, lips and skin were normal. Death from coronary thrombosis occurred 6 months later.

Comment. This patient developed mouth and skin lesions and evidence of a diffuse disseminated neuropathy of the brain and spinal cord after treatment of diabetes had been instituted. The tongue lesion and psychosis suggested a vitamin deficiency of pellagrous nature. Following prolonged vitamin B therapy there was complete mental recovery, with disappearance of the skin and mouth lesions, but some neurologic residual persisted.

Case 2. L. P. (B. I. H. 13642A), a 67-year-old man with mild diabetes of 4 years' duration, was admitted to the hospital in August, 1940, for herniorrhaphy. The urine was sugar-free, and the blood-sugar level was normal. Following operation he developed urinary retention due to prostatism. He was unable to eat and received several intravenous infusions of glucose but no vitamins. He became anemic and lost weight. One month later it was discovered that he had developed foot drop on the right and weakness of the left foot. The diabetes had been under control without insulin throughout the hospital stay.

Examination revealed weakness of the dorsiflexors of the feet, with complete foot drop on the right and diminution of sensation in the distribution of the peroneal nerve. There was marked diminution in the vibratory sensation in both lower legs, and the ankle jerks were hypoactive.

The patient was given a high-vitamin diet with a concentrated vitamin B complex preparation by mouth and injections of 30 mg. of thiamine chloride daily for 1 month. The right lower leg was put in a cast and later was fitted with a brace. Motor power gradually returned, and the brace was discarded after 6 months. Four years later there were no neurologic symptoms or signs. Muscle power in both feet was good. The knee jerks and ankle jerks were active and equal. There was no sensory defect. Vibratory sensation in both feet was normal.

Comment. In this patient with mild diabetes under constant control, neurologic symptoms developed as a result of a combination of insufficient food and vitamin intake, together with frequent glucose infusions and anemia. Recovery was subjectively and objectively complete after 6 months of intensive vitamin therapy.

Case 3. E. C. (B. I. H. 39066A), a 37-year-old man with a history of chronic alcoholism, was first seen in June, 1935, with symptoms of diabetes of 1 year's duration, during which time he had lost 74 pounds in weight. The diabetes was controlled in 2 weeks by diet and insulin. At the end of that time the patient complained of pains and paresthesias, first in the right arm and neck and later in the groins, scrotum and outer aspect of the right thigh. He also had paroxysmal attacks of girdlelike pain around the chest and severe burning sensations in the lower extremities and genitalia, especially at night. He complained of general weakness and repeatedly had to return to bed. He continued to lose weight on a high-calorie, high-carbohydrate diet, despite a marked improvement in the diabetes and a reduction in the insulin requirement from 60 to 6 units a day.

Early in the illness, neurologic examination revealed only absence of ankle jerks, but later there developed inequality of knee jerks and weakness and hyperesthesia of both lower extremities.

From the beginning, the patient had been given in addition to a proper diet and insulin large amounts of Harris's yeast powder by mouth. After 4 months of this therapy marked subjective improvement began. In 6 months he was free of neurologic complaints and had regained 10 pounds in weight.

Comment. In this alcoholic patient, the acute symptoms of diabetes had been present for over a year with marked loss of weight. The neurologic manifestations, however, developed 2 weeks after the treatment of diabetes was begun and for a while became progressively worse in spite of complete control and marked improvement of the diabetes. The subjective manifestations of neuropathy preceded by some months the objective signs, but they all finally cleared after 6 months of yeast therapy.

Case 4. H. V. (B. I. H. 29225), a 54-year-old woman with a history of diabetes treated by diet alone, was admitted to the hospital in November, 1935, in diabetic coma. She had recently lost 20 pounds in weight. Ten days after recovery from the coma, and after the diabetes had been satisfactorily controlled, she complained of excruciating paroxysmal pain in the lower back, especially on the right, and in both thighs, requiring the frequent administration of morphine. Examination revealed absence of tendon reflexes in the arms and legs, a sensory level at the 12th thoracic segment and loss of vibratory sensation below this level. One month later, when allowed to get out of bed, the patient showed unsteadiness of gait and ataxia of the legs and was unable to walk without support. She also displayed marked weakness and atrophy of the muscles of both legs, diminution of vibration sense on the right, loss of position sense in both feet, a positive Rom-

berg sign and absence of deep reflexes. The weight was only 98 pounds. Spinal-fluid examination was negative except for a total protein content of 78 mg. per 100 cc.

Following discharge from the hospital the patient continued on a high-calorie, high-vitamin diet with yeast tablets and iron. The diabetes was controlled by diet and insulin. Six months after the development of the neuropathy, the gait was greatly improved and she was able to walk downstairs without support. The Romberg sign was negative, but the knee jerks were still absent. In the next 18 months she gained 37 pounds. Six years after the onset of the neuropathy there were no neurologic symptoms except occasional cramps in the calves at night. Both knee jerks and the right ankle jerk had returned, and position sense had become normal. Vibration sense, however, was still impaired below the ankles — more on the right than on the left.

Comment. This patient developed symptoms and signs of severe peripheral neuropathy and of myelopathy immediately following the control of diabetic coma. The symptoms of myelopathy preceded the detection of objective abnormalities and disappeared before the latter cleared up. Almost complete recovery from both was noted 6 months after vitamin therapy was begun, and relatively normal health was maintained for 6 years.

Case 5. D. S. (B. I. H. 48219A), a 25-year-old man, was first seen in July, 1937, while in mild diabetic acidosis. The diabetes had been poorly controlled for 8 years. During the previous 6 months he had had intermittent swelling of the legs and fleeting pains in the legs and back. During the last 2 months he had had anorexia and nausea and had lost 25 pounds in weight. Examination disclosed diminished knee jerks, hyperesthesia of the lower extremities and tenderness of the calves.

During the next 2 months, while the diabetes was fairly well controlled, there gradually developed painful paresthesias in the chest, abdomen and arms in addition to those in the legs. Walking was difficult because of the paresthesias of the feet. Growing difficulty in controlling the diabetes led to the disclosure of pulmonary tuberculosis by x-ray examination. At this time the patient had hyperesthesia involving all the extremities and the trunk. There was hyperhidrosis below the level of the 12th dorsal segment. The left ankle jerk was absent, and the left knee jerk could be obtained only by reinforcement. The tongue was beefy and smooth. The spinal-fluid total protein was 90 mg. per 100 cc., and the gold-sol curve was 2332211000.

During the next 3 weeks the patient received daily injections of 10 cc. of crude liver extract and 3.3 mg. of thiamine chloride, together with 12 yeast tablets. The latter were soon omitted because of severe diarrhea. After transfer to a tuberculosis sanatorium, injection of thiamine chloride in doses of 6.6 mg. were continued daily for a few weeks; the dosage was then decreased to 10 mg. every other day for 6 months. At the end of that time there was definite improvement in the paresthesias but the ankle jerks were absent. Vibration and position sense remained intact. The glossitis had disappeared. Several months later the patient was completely free of neurologic signs and symptoms. He was then receiving daily 15 yeast tablets, 3 cod-liver oil tablets and 3 mg. of thiamine chloride orally. He continued this treatment, and when seen 4 years later still had no complaints and showed no neurologic abnormalities.

Comment. In this case the neurologic symptoms began while the diabetes was out of control and became more pronounced following regulation of the diabetes. The subjective improvement preceded the disappearance of objective neurologic abnormalities. Under intensive vitamin therapy, definite subjective improvement occurred after 4 months and was followed by complete recovery in 1 year. It is worthy of note that the neuropathy continued to improve while under treatment with parenteral thiamine, despite a period of omission of oral yeast therapy because of diarrhea.

Case 6. I. C. (B. I. H. 64290A), a 59-year-old woman, was found in November, 1940, to have diabetes. During the next 2 months, while the diabetes was being controlled by diet and insulin, she complained of anorexia, weight loss, crampy pain in the epigastrium and precordium and pains and paresthesias in the lower extremities. The right knee jerk was absent, and there was diminished vibration sense in both legs, more marked in the left than in the right.

Because of the persistence of abdominal pain, anorexia and continued weight loss, repeated gastrointestinal studies were carried out during the ensuing 4 months. These were negative except for a suspicion of small stones in the gall bladder. Blood-cell counts, the sedimentation rate, the blood chemical findings and the basal metabolism were normal. A blood Hinton reaction was negative. Examination of the spinal fluid on two occasions showed total protein contents of 167 and 182 mg. per 100 cc. but no other abnormalities. During these 4 months the diabetes was under constant control.

The patient received an intensive 2-week course of vitamin therapy consisting of 20 mg. of thiamine chloride and 2 cc. of vitamin B complex parenterally each day. For the next 6 weeks she was bedridden because of weakness of the legs and received no vitamins. The abdominal pain continued, but the diabetes remained under control and there was no change in weight. At the end of the 6-week period there was weakness of the lower extremities and an unsteady gait, and the patient had difficulty in rising from a chair. Both knee jerks and ankle jerks were absent. There was moderate tenderness of the calves and thighs. The paresthesias in the left foot had disappeared.

During the next 6 months 25 mg. of thiamine chloride parenterally and 15 yeast tablets were given daily. The appetite improved, and there was a gain in weight. The abdominal pain gradually subsided, and at the end of the 6 months the patient was free of subjective complaints. During the next 2 months she received only 12 mg. of thiamine chloride twice weekly, the dosage of yeast tablets remaining unchanged. Three months later she had gained 22 pounds, felt well and had no difficulty in walking. Three years later she was still in good health. The knee jerks were present and equal, but vibration sense in both legs was still diminished.

Comment. In this case myelopathy developed soon after the control of an acute stage of diabetes that was accompanied by marked loss of weight. The symptoms of abdominal pain, loss of weight, anorexia and weakness suggested gastrointestinal malignancy, but the neurologic examination warranted the diagnosis of diabetic neuropathy after malignancy had been ruled out. Subjective neurologic complaints preceded the objective signs and disappeared first.

Clinical recovery followed 6 months of vitamin therapy.

Case 7. H. G. (B. I. H. 65326A), a 46-year-old man, was first seen in April, 1941, with acute manifestations of diabetes mellitus, which had been discovered 18 months before. He had had for 1 year paresthesias and weakness of both feet and more recently intermittent claudication, especially of the left leg. Pulsation of the left dorsalis pedis artery could not be distinctly felt. Calcification of the arteries of the legs could not be demonstrated by x-ray examination.

Four months later the intermittent claudication of the left leg had become severer. The patient also complained of weakness in the left foot. The diabetes had been incompletely controlled by diet and insulin. Examination showed sluggish jerks and ankle jerks and a diminution of vibratory sensation in both legs.

One month after daily injections of 25 mg. of thiamine chloride and daily feeding of 15 yeast tablets had been begun, the patient was able to walk four times as far as previously. After 3 months of this therapy the intermittent claudication and all other neurologic symptoms cleared up completely, although the diabetes remained poorly controlled.

Comment. In this case the neuropathy developed during an acute stage of diabetes. It became worse after insulin was begun and progressed for 4 months until thiamine and yeast were administered. The symptoms then disappeared within 3 months, only to recur 2 years later after a long period of poor diabetic control and omission of vitamin therapy. Intermittent claudication was a possible manifestation of thiamine deficiency; it was not attributable to peripheral vascular sclerosis.

Case 8. S. C. (B. I. H. 43964A), a 74-year-old woman, was first seen in April, 1943, after many years of diabetes controlled by diet and insulin. Three weeks before entry she developed bronchopneumonia and was successfully treated with sulfadiazine. During convalescence, however, she developed nausea, vomiting, anorexia and incontinence of feces and urine. The tongue was smooth along the edges and red. There was a large, noninfected bedsore over the right iliac crest. The rectal sphincter was patulous and without tone.

There was a large fecal impaction, and the mucosa of the rectum was prolapsed. The knee jerks were absent. The diabetes was under control.

The patient was given a daily dosage of 2 cc. of vitamin B complex, 100 mg. of nicotinamide and 120 mg. of thiamine chloride parenterally. After 18 days the fecal and urinary incontinence disappeared and the decubitus ulcer completely healed. The patient continued to receive 2 cc. of vitamin B complex parenterally each day. Two months after discharge the knee jerks were hyperactive, vibratory sensation was normal, and there was no incontinence. Fifteen months later no neurologic disturbances had recurred.

Comment. This is a case of an acute onset of diabetic neuropathy with manifestations of a vitamin B complex deficiency and rapid recovery following parenteral vitamin B therapy.

Discussion

There appears to be no direct relation between the duration or severity of diabetes and the presence of neuropathy. The relation of neuropathy, however, to the onset, exacerbations and treatment of diabetes is of special interest and importance. In a few cases, the neurologic abnormalities develop before glycosuria is discovered. In others, they appear during the acute stage of diabetes (Cases 2, 3 and 6). In still others, they appear to be precipitated by other complications of the diabetes (Cases 5 and 8) or by the control of diabetes, whether by diet alone or by diet and insulin (Cases 1, 3, 4 and 6).

In most patients with diabetic neuropathy, there are observed many of the manifestations of experimentally induced thiamine deficiency in man, such as easy fatigability, forgetfulness, irritability, nausea, weight loss and personality changes (Cases 5 and 6). There may be evidence of additional deficiency of nicotinic acid, of riboflavin or of both (Cases 1, 5 and 8), for manifestations of deficiency of the vitamin B complex are frequent in diabetic patients.[24–26] Moreover, the progression, disappearance and recurrence of the neuropathy parallel the course of other manifestations of deficiency of the vitamin B complex as altered or influenced by vitamin therapy (Cases 1 and 5). Since many patients with diabetic neuropathy frequently fail to improve on thiamine alone, they should be treated with the entire vitamin B complex in addition, parenterally if necessary.

Whatever may be the relation of diabetes to neuropathy or to vitamin deficiency, particularly to deficiency of thiamine, the importance of the latter to the physiologic activity of nerve tissue has been demonstrated by Nachmanson and Steinbach.[27] These authors showed that thiamine is essential to the oxidation of pyruvic acid, a reaction that in turn provides the acetate required for the formation of acetylcholine. Since acetylcholine is necessary for the conduction and transmission of nerve impulses, a decrease in the rate of formation of this substance may lead to the motor disturbances observed in diabetic neuropathy. Other mechanisms, such as functional or organic changes in the myelin sheaths,[11] must be postulated to explain the sensory changes that are also found.

Although the manifestations of vitamin B complex deficiency associated with uncomplicated poor nutrition are typical and respond dramatically to specific therapy,[28] the manifestations of the same deficiencies in diabetic patients are often atypical, frequently occur with apparently adequate diets and usually respond more slowly to the same treatment than in patients without such diabetes. These differences suggest a basic physiologic difference in the mechanism by which the deficiency manifestations are produced.

Govier and Greig[29–31] showed that in shocked or anoxic dogs cocarboxylase might dephosphorylate and become inactive. Similar inactivation of coenzyme I and of alloxazine adenine dinucleotide also occurred. The administration of large amounts of thiamine, riboflavin and nicotinamide resulted in the resynthesis of the respective coenzymes. Since these substances ultimately function as coenzymes in carbohydrate metabolism, it is possible that in diabetes a comparable metabolic disturbance underlies the manifestations of vitamin B complex deficiency and their improvement through large doses of vitamin B complex.

In nondiabetic patients, recovery from polyneuropathy induced by diets partially deficient in thiamine requires many months of thiamine therapy.[21] It is therefore not surprising that recovery from diabetic neuropathy is often slow, particularly since the process when first recognized may have been of long duration. Hence, treatment of diabetic neuropathy may have to be continued for several years (Case 1) with massive doses of thiamine and of vitamin B complex parenterally before the process is arrested or alleviated. In an analogous situation, the combined system disease of pernicious anemia responds even more slowly to treatment than does diabetic neuropathy. At a very early stage, however, the diabetic neuropathy may still be of a functional or biochemical nature and may therefore respond quite rapidly to specific treatment.

Summary and Conclusions

Diabetic neuropathy is a disseminated neurologic disturbance that may involve any part of the nervous system.

The mere control of glycosuria, with or without insulin, does not prevent the development of diabetic neuropathy. The chronic and severer manifestations of diabetic neuropathy demand intensive and prolonged therapy.

The treatment of choice consists of large doses of thiamine chloride and vitamin B complex, parenterally if necessary, in addition to control of the diabetes.

The prognosis for recovery from diabetic neuropathy is fair, and in some cases even good.

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PNEUMOCOCCAL PERICARDITIS TREATED WITH INTRAPERICARDIAL PENICILLIN*

Report of a Case

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THE effectiveness of penicillin in the treatment of many varieties of pneumococcal infections is well established. Since it is believed that its effectiveness in a proved case of pneumococcal pericarditis is worth recording, the following case is presented.

F. D., a 30-year-old shipyard office worker, was admitted to the Northern Permanente Foundation Hospital on April 8, 1945, complaining of severe knifelike chest pains and dyspnea. Four weeks prior to admission he developed pleuritis on the left side, associated with some coughing, which was relieved by heat and strapping. Three weeks prior to admission he developed substernal pain, which was made worse by coughing. Severe dyspnea and orthopnea were present for 3 weeks, becoming progressively worse, but there was no ankle swelling. There was fever during the week prior to admission, the temperature rising as high as 104° F., but no severe shaking chill. Three weeks prior to admission a tooth was extracted. The past and family histories were noncontributory.

Physical examination revealed an extremely dyspneic and orthopneic man, who was moderately apprehensive. There was a granulating tooth socket in the right upper jaw, without drainage. The lungs showed dullness and diminished breath sounds over the left lower lobe posteriorly. Cardiac dullness extended to the anterior axillary line. The point of maximum impulse was not palpable. The heart sounds were faint and distant. Sinus tachycardia was present. In the 2nd interspace at the left sternal border was a loud to-and-fro pericardial friction sound, transmitted to the apex but faint there. The liver and spleen were not felt. There was no edema.

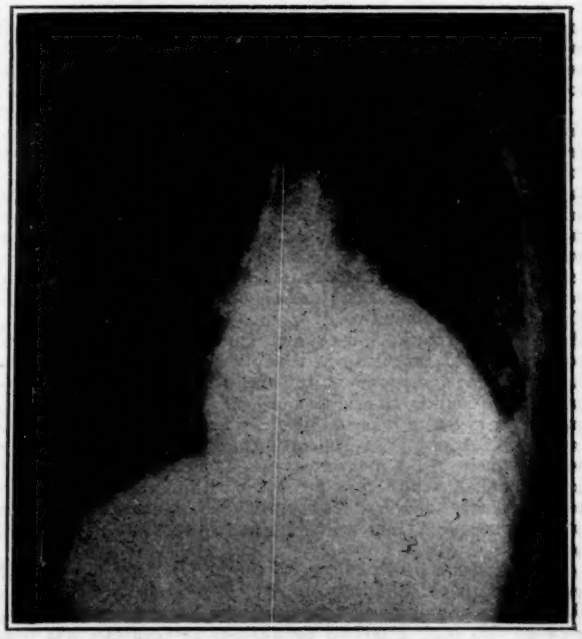

Figure 1.

The temperature was 103°F., the pulse 130, the respirations 32, and the blood pressure 110/80. The white-cell count was 19,500, with 84 per cent neutrophils, 8 per cent of which were

*From the Northern Permanente Foundation, Vancouver, Washington.

stab cells. The red-cell count was 4,600,000 and the hemoglobin 13.2 gm.

An x-ray film taken on admission (Fig. 1) was interpreted as compatible with a pericardial effusion, left pleural effusion and vascular engorgement. An electrocardiogram showed no

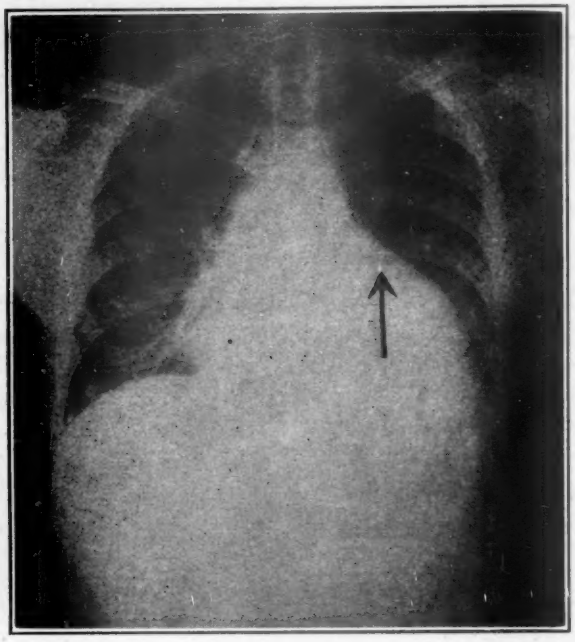

FIGURE 2.

specific evidence of pericarditis, and the voltage was within normal limits; T_2 was diphasic. A blood culture was sterile. The venous pressure was equivalent to 160 mm. of saline solution.

The patient was given 10,000 units of penicillin every 3 hours intramuscularly and full doses of sulfadiazine with sodium bicarbonate, on the presumption that the infection might be a coccal one, and supportive therapy consisting essentially of oxygen and morphine, which made him more comfortable.

On the premise that a purulent pericarditis was a possibility, and since it is known that coccal infections of serous cavities, such as the pleural, subarachnoid and synovial types, respond to locally introduced penicillin, it was decided to do a pericardial paracentesis and instill penicillin. The tap was done on the day of admission in the 5th anterior interspace at the midclavicular line, with novocain infiltration. Since fluid was obtained with the infiltrating 22-gauge needle, the procedure was continued without removing the needle. One hundred cubic centimeters of a thin sanguineous fluid was removed. Twenty thousand units of penicillin were injected, even though the bacteriologic character of the fluid had not yet been evaluated, since it was thought that no harm could result and that a subsequent tap could be avoided should organisms be found. In addition, 10 cc. of air was instilled and another x-ray film was obtained. The fluid level then seen in the pericardium (Fig. 2) proved that the fluid was not being withdrawn from the pleural cavity. It contained 250,000 red cells and 2500 white cells per cubic millimeter, with 90 per cent polymorphonuclear leukocytes. No organisms were seen in a gram-stained smear, and an acid-fast stain was also negative.

In 36 hours a broth culture of the pericardial fluid yielded a gram-positive diplococcus, which examination by the *Quelling* technic showed to be a Type 8 pneumococcus. In view of this fact, a second pericardial paracentesis was performed on April 10 with a 22-gauge needle, and 150 cc. of fluid was removed, 15,000 units of penicillin being inserted. The fluid had a specific gravity of 1.020 and contained 94,000 red cells and 11,000 white cells per cubic millimeter, with 88 per cent polymorphonuclear leukocytes. No organisms were found in the smear, and a culture was sterile.

The penicillin dosage was increased to 20,000 units every 3 hours. The patient improved gradually, but remained febrile. On the 5th day, because of x-ray evidence of increasing effusion at the base of the left lung, a thoracentesis was performed and 500 cc. of a deep yellow fluid was removed with ease. The fluid clotted on standing, so that a cell count could not be obtained. A gram stain and culture were negative. No acid-fast organisms were found.

The venous pressure on the 6th day was equivalent to 96 mm. of saline solution. After running a low-grade fever for several days, the patient became afebrile on the 10th day, remaining so thereafter. Chemotherapy was discontinued on the 12th day. The pericardial friction was not heard after the 8th day. The remainder of the course was uneventful, and the patient was discharged on April 30, the 20th hospital day. When seen again on June 14, 1945, he was asymptomatic and was working. The cardiac examination and follow-up x-ray examination (Fig. 3) were both negative.

Although it cannot be stated with certainty that the intrapericardial penicillin was responsible for the cure of this patient, it is fair to assume that it played an important contributory role. This assumption seems justified in view of the fact that it is well known that the treatment of pleural and synovial infections is much more successful when

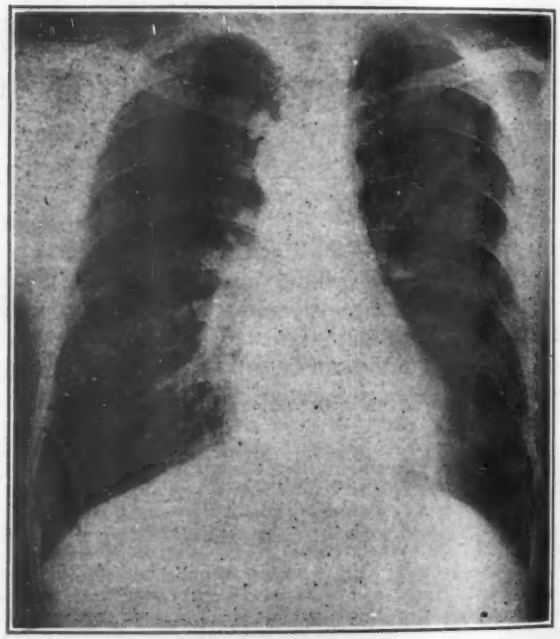

FIGURE 3.

the local use of penicillin supplements parenteral penicillin.

SUMMARY

A case of Type 8 pneumococcus pericarditis successfully treated with penicillin intrapericardially, as well as with sulfadiazine and intramuscular penicillin, is presented.

MEDICAL PROGRESS

HEMOGLOBINEMIA AND THE HEMOGLOBINURIAS*

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BLACKWATER, or more scientifically, hemoglobinuria, attracts the attention of patient and physician as do few other symptoms. Indeed, few other symptoms indicate so serious a disturbance of body processes or carry so grave a prognosis. The diseases producing or associated with hemoglobinuria, with some exceptions, usually either have a high fatality rate or are extremely chronic and disabling.

It is the purpose of this paper to review the mechanisms by which hemoglobinuria is produced, to consider its pathologic effects and to summarize the important features of the clinical syndromes that lead to the excretion of hemoglobin in the urine.

PATHOLOGIC PHYSIOLOGY OF HEMOGLOBINEMIA AND HEMOGLOBINURIA

Normally in the human adult approximately 1.9 per cent of the circulating erythrocytes are destroyed each twenty-four hours, resulting in the liberation of between 7 and 8 gm. of hemoglobin. Destruction of these erythrocytes takes place in the cells of the reticuloendothelial system, and the hemoglobin released as a result of their breakdown is metabolized by the reticuloendothelial cells into bilirubin, which is subsequently excreted in the bile by the polygonal cells of the liver. Theoretically, this process is an intracellular one and hemoglobin does not escape into the circulating blood plasma. Actually, however, 100 cc. of normal human plasma contains 2 to 5 mg. of heme-containing pigment derived, perhaps, from actual "intravascular" breakdown of erythrocytes.

In certain disease states, the rate of erythrocytic breakdown sometimes is increased by as much as fiftyfold, with liberation of 400 to 500 gm. of hemoglobin within a period of twenty-four hours. In some conditions, for example, familial hemolytic jaundice, the erythrocyte destruction and hemoglobin breakdown continue as an intracellular process and the increased pigment catabolism is reflected only by an elevation of the plasma bilirubin concentration and an increased excretion of bilirubin. In other diseases, such as the acute hemolytic processes encountered in sulfonamide toxicity or incompatible blood transfusions, the destruction of erythrocytes occurs intravascularly without the aid of the reticuloendothelial system. Hemoglobin is liberated directly into the blood plasma, with the result that its concentration in the plasma may increase to 400 or 500 mg. per 100 cc., or higher. Hemoglobinemia may occur as a result of many different factors, but the mechanics of pigment metabolism are much the same, regardless of the primary cause of the hemolytic mechanism.

Hemoglobin liberated intravascularly first appears in the plasma as oxyhemoglobin, and if its concentration in the plasma is relatively low (50 to 100 mg. per 100 cc.), this is the only pigment that can be detected spectroscopically. Small amounts of oxyhemoglobin are rapidly removed from the blood plasma in four or five hours — primarily by the reticuloendothelial system. If, however, hemolysis is so extensive that large amounts (200 to 500 mg. per 100 cc.) of hemoglobin accumulate and remain in the plasma, an entirely different set of circumstances ensues. The hemoglobin molecule breaks down into hematin (the iron-porphyrin pigment complex) and globin (the protein fraction of hemoglobin). The hematin immediately combines with plasma albumin, and a new pigment, methemalbumin, is formed. There is good experimental evidence that oxyhemoglobinemia is innocuous, but it is quite possible that methemalbumin exerts a toxic effect on various organs and tissues.

Methemalbumin was first described by Fairley and Bromfield,[1, 2] who noted its presence in several cases of severe blackwater fever. It should not be confused with methemoglobin, which is usually intraerythrocytic in location and is rarely present in the plasma. In contrast, methemalbumin is encountered only in the plasma. Although methemalbumin resembles methemoglobin in the fact that the iron molecule in the prosthetic group of both compounds is in the oxidized or ferric state, its presence in the blood has an entirely different diagnostic and prognostic significance.[3, 4] Small amounts of methemoglobin occur normally in human blood,[5] but methemalbumin never occurs normally and is encountered only in conditions of severe intravascular hemolysis with prolonged high concentrations of hemoglobin in the plasma. Methemoglobin is readily reconverted to oxyhemoglobin in the red blood cell,[6] but methemalbumin cannot be reconverted either to methemoglobin or to oxyhemoglobin, and must be disposed of by the body in some other fashion, presumably by the reticuloendothelial system through conversion to bilirubin.[3, 4]

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Sulfhemoglobin, a third abnormal blood pigment, is encountered even more rarely than methemoglobin or methemalbumin. Like methemoglobin, it almost always is an intraerythrocytic pigment, but it occasionally occurs in the plasma in certain hemolytic diseases with associated intoxications.[8]

Myoglobin and its ferri-derivative, metmyoglobin, appear in the urine following crushing injuries, but owing to the rapid rate at which these substances are removed from the blood stream, it is unusual to detect them in the blood plasma.[7]

Detection of these abnormal heme pigments is a simple matter, and frequently may be of considerable value in diagnosis and prognosis. Methemalbumin, methemoglobin, sulfhemoglobin and metmyoglobin are characterized by a distinct absorption band in the red portion of the spectrum, and the presence of such a band may be readily demonstrated with an inexpensive hand spectroscope, frequently by the simple expedient of sighting the instrument through the well illuminated auricula or lobe of the ear. The absorption maximums of the various heme pigments are listed in Table 1. Although the alpha bands of the various metcompounds have characteristic wave lengths, they differ in situation by only a few Angström units,

TABLE 1. *Absorption Maximums of Heme Pigments.*

PIGMENT	WAVELENGTH OF ABSORPTION MAXIMUMS		
	ALPHA	BETA	GAMMA
	millimicrons	*millimicrons*	*millimicrons*
Metmyoglobin	636	580	—
Methemoglobin	630	576	541
Methemalbumin	623–624	540–541	500–501
Sulfhemoglobin	618–620	540	—
Myoglobin	581–582	545–546	—
Oxyhemoglobin	576	541	—

and with the spectroscopic instruments commonly available, it is difficult to differentiate one from another. Consequently, a few simple chemical tests are necessary to identify definitely the abnormal pigment once its presence in the blood, plasma or urine has been established. These tests depend on the dispersion or persistence of the alpha bands of the compound when a reducing or oxidizing agent is added to the solution. Such tests are outlined in Table 2.

When hemolysis is extensive or occurs rapidly, the concentration of hemoglobin in the plasma rises to high levels and hemoglobin appears in the urine. Since the hemoglobin molecule is approximately the same size as the plasma albumin molecule, and since hemoglobin is excreted freely by the normal kidney and albumin is not, it has been difficult to reconcile this phenomenon with the modern concept of glomerular filtration, that is, with the concept that the fundamental process in urine secretion is the formation by the glomerulus of a protein-free filtrate containing diffusible constituents of plasma in the same concentration as they exist in the plasma water.

The best explanation of the mechanism by which hemoglobin is excreted by the kidney was advanced by Havill, Lichty, Taylor and Whipple,[9] subsequently elaborated by Monke and Yuile[10] and summarized in an excellent review by Yuile.[11] Carrying out their investigations in dogs, these investigators found that there was a definite renal threshold for the excretion of hemoglobin. No hemoglobin could be detected in the urine when the plasma hemoglobin concentration was below 100 mg. per 100 cc., but when it exceeded 100 mg. per 100 cc., hemoglobin appeared in the urine. At concentrations in excess of 250 mg. per 100 cc., the rate of hemoglobin excretion varied directly with the concentration of hemoglobin in the plasma. Furthermore, by performing hemoglobin and creatinine clearance studies simultaneously, Monke and Yuile[10] showed that when the plasma hemoglobin concentration was in excess of 250 mg. per 100 cc. the rate at which hemoglobin was excreted was always 3 per cent of the creatinine clearance.

TABLE 2. *Differentiation of Abnormal Blood Pigments in Serum, Blood or Urine.**

REAGENT	PIGMENT AND POSITION OF ALPHA ABSORPTION MAXIMUM		
	METHEMOGLOBIN (630 millimicrons)	METHEMALBUMIN (623–624 millimicrons)	SULFHEMOGLOBIN (618–620 millimicrons)
Sodium cyanide, 5%	Dispersed	Unaltered	Unaltered
Hydrogen peroxide, 3%	Dispersed	Unaltered	Dispersed
Stokes' reagent (2 drops added to 1 cc.)	Dispersed	Unaltered	Unaltered
Ammonium sulfide, 10% (1 drop added to 1 cc.)	Dispersed	Unaltered	Unaltered
Ammonium sulfide, concentrated (0.1 cc. added to 1 cc.)	Dispersed	Dispersed	Unaltered

*Modified from Fairley[4] and Fox.[8]

These observations could best be explained by assuming that 3 per cent of the pores in the glomerular membrane were large enough to allow the passage of large hemoglobin molecules into the glomerular filtrate. As the filtrate passed down the renal tubules, the epithelial cells of the proximal convoluted tubules removed the hemoglobin molecules by a process that has been called "arthrocytosis." So long as the amount of hemoglobin passing through the glomerular membrane did not exceed 2 or 3 mg. per minute, the epithelial cells recovered all the hemoglobin and hemoglobinuria did not occur. The capacity of these cells to take up hemoglobin was limited, however, and if larger amounts of hemoglobin leaked through the glomerulus, they were unable to assimilate it and hemoglobin appeared in the urine. The recovery capacity of the tubules was completely exceeded when the plasma concentration of hemoglobin exceeded 250 mg. per 100 cc., and any further increase in the concentration in the plasma was reflected by a proportional increase of hemoglobin in the urine.

The tubular epithelial cells thus play an active role in the conservation of hemoglobin and iron.

Deposits of iron-containing pigment can readily be demonstrated in these cells after injections of hemoglobin, and the iron content of the kidney is markedly increased following multiple injections of hemoglobin.[13] Presumably this iron is eventually returned to the body for reuse in hemoglobin synthesis.

If the tubular cells become filled with iron containing pigment, their capacity to absorb hemoglobin is interfered with, and as a consequence the renal threshold for hemoglobin may fall by as much as 60 per cent.[13, 14] Such a decrease in threshold is seen following repeated injections of hemoglobin and in certain cases of chronic hemoglobinuria, for example, paroxysmal nocturnal hemoglobinuria. In the latter, the tubular cells become so filled with iron-containing pigment that they are cast off and appear in the urine, where they may be readily identified.

When excreted in alkaline urine, hemoglobin is found chiefly as oxyhemoglobin. In acid urine, and in urine that remains in the bladder or is allowed to stand in vitro for any length of time, considerable amounts of methemoglobin are found.

The mechanism of excretion of myoglobin probably is similar to that of hemoglobin, but because its molecular weight is only 17,500 in contrast to 68,000 for hemoglobin, there is a marked quantitative difference. The threshold for renal excretion of myoglobin is only 20 mg. per 100 cc. of plasma, and the rate of clearance is twenty-five times more rapid than that of hemoglobin. Consequently, myoglobin is removed from the blood stream so rapidly that it is difficult to demonstrate it in the blood plasma.[15]

Pathologic Effects of Hemoglobinemia and Hemoglobinuria

The sequence of hemoglobinuria, anuria, uremia and death following transfusion of incompatible blood[16–18] and in blackwater fever[19] as well as the demonstration of tubular occlusion by hemoglobin casts in the kidneys of such cases, led to the belief that passage of hemoglobin through the kidney produced serious and irreversible renal damage. Considerable experimental evidence supported this hypothesis.[20–23] Yorke and Nauss,[20] Baker and Dodds[21] and DeGowin et al.[22, 23] injected solutions of hemolyzed erythrocytes into experimental animals (rabbits and dogs) and reported that these animals frequently became anuric, developed uremia and died of renal failure if the urine was acid during the period of hemoglobinuria. If the urine was alkaline in reaction, there were no ill effects from the excretion of hemoglobin.

Histologic examinations showed that many renal tubules were occluded with hemoglobin casts in those animals that had had an acid urine, but that the kidneys were relatively normal in animals whose urine had been alkaline. Observations such as these indicated that hemoglobin damaged the kidney only if the urine was acid during the period of hemoglobinuria, and explained this damage as due to the precipitation of acid hematin in the renal tubules, with subsequent mechanical blockage of urine flow. This theory led to the widespread therapeutic use of alkalies in an attempt to alkalinize the urine in patients with hemoglobinuria from transfusion reactions,[17] blackwater fever[24] or other causes.

In marked contrast to these observations are numerous experiments that have conclusively demonstrated that solutions of pure hemoglobin can be injected intravenously into normal human subjects and into experimental animals without producing any significant impairment of renal function, regardless of the reaction of the urine.[9, 25–31] Many of these studies have been performed within the last five years and have been made with carefully prepared solutions of hemoglobin, in some instances with pure crystalline hemoglobin. Careful observations of the clinical condition of the subjects revealed that as much as 20 gm. of hemoglobin might be administered without any ill effect. In some cases abdominal cramps and fever occurred, but these well might have been caused by the presence of histamine-like substances or potassium in the hemoglobin preparations employed.[30] The most thorough evaluation of the effect of hemoglobinemia, myoglobinemia and methemoglobinemia on kidney function has been made by Bing.[31] Solutions of pure crystalline hemoglobin, myoglobin and methemoglobin were infused into normal dogs and into dogs made acidotic by the oral administration of ammonium chloride. Studies were made of the glomerular filtration rate and of the effective renal plasma flow in all animals, and in some experiments tubular reabsorptive capacity also was measured. Following infusion of large amounts of hemoglobin and myoglobin there was no significant variation in renal function, and histologic examination revealed no lesions of any type, even in those animals in which the reaction of the blood had been reduced to pH 6.90. Injections of methemoglobin produced no functional or anatomic changes in normal dogs, but in all the animals that were acidotic, methemoglobinemia and methemoglobinuria produced a marked decrease in clearance values (10 per cent of the control values), the absorptive capacity of the renal tubules for glucose decreased, nitrogen was retained, and the dogs rapidly became moribund. Histologic examination of the kidneys of the acidotic animals revealed marked tubular necrosis, but pigmented casts were found in the tubular lumens only in those acidotic animals that received repeated infusions of methemoglobin after renal failure had been initiated. These observations indicated that the precipitation of hemoglobin products in the tubules, far from being an important cause of anuria and renal failure, was actually the result of a decreased volume of urine

and renal failure. De Navasquez[28] made somewhat similar observations on human subjects and on rabbits and concluded that the excretion of hemoglobin, even in acid urine, did not impair renal function and that renal damage occurring in transfusion reactions was brought about not by tubular blockage but by greatly decreased blood flow through the kidney and by tubular anoxemia.

Of considerable interest in this connection are the observations of Mason and Mann[32] and Hesse and Filatov,[33] who showed that injections of hemoglobin solutions produced marked spasm of renal blood vessels, disappearance of about half the working glomeruli and a marked and rapid decrease in the size of the kidney.

Thus, the best available evidence indicates that in normal persons, hemoglobinemia and the excretion of moderate amounts of hemoglobin are without ill effects, regardless of the reaction of the urine. The fact remains, however, that extreme intravascular hemolysis frequently is associated with fatal renal damage. This damage is probably produced by shock-like levels of blood pressure and by severe and prolonged reduction of blood flow through the kidney. Decrease in renal blood flow is accentuated by hemoglobinemia, and in cases of marked reduction in the alkali reserve, the formation of methemoglobin in the acid glomerular filtrate may aggravate already existing tubular damage. Similar conclusions have been reached by Foy, Altmann, Barnes and Kondi[34] in an excellent and extensive review of all published observations on hemoglobinuria.

In addition to the renal lesions observed in severe intravascular hemolysis, extensive central hemorrhagic necrosis of the liver has been reported,[16, 23] a lesion that might also be produced by low blood pressure, decreased blood flow and anoxemia.

Paroxysmal Cold Hemoglobinuria

Clear differentiation of hematuria and hemoglobinuria was made in 1854 by Dressler,[35] who described a case of paroxysmal hemoglobinuria in a patient with congenital syphilis but did not recognize the etiologic importance either of syphilis or of chilling. In 1866, Gull[36] observed that exposure to cold precipitated attacks of hemoglobinuria, but he assumed that the shaking chill was instrumental in producing the hemoglobinuria. Rosenbach[37] reported that an attack of hemoglobinuria could be precipitated by immersing the patient's feet in cold water for ten minutes, thus clearly proving the causal relation of chilling to the syndrome. This procedure, now known as the "Rosenbach test," is of considerable value as a diagnostic procedure in differentiating cold hemoglobinuria from various other types of hemoglobinuria, but it is occasionally dangerous because of the severity of the paroxysms produced. Ehrlich[38] found that the phenomenon of hemoglobinemia could be produced locally in susceptible persons by placing a ligature around a finger and then immersing it in ice water, free hemoglobin being demonstrated in the serum of blood removed from the finger. This, the "Ehrlich test," is less hazardous to the well being of the subject than the Rosenbach test and should be performed before the latter in the investigation of patients with hemoglobinuria.

Götze[39] first recognized the significance of syphilis as the cause of cold hemoglobinuria, and subsequent investigations have indicated that the disease is usually, perhaps always, a manifestation of syphilitic infection. Donath and Landsteiner[40] reviewed the literature from 1905 to 1925 and found that of 99 cases reported, 95 had either clinical or serologic evidence of syphilis. All of Mackenzie's[41] 5 cases showed positive Wassermann reactions, and almost all the cases subsequently reported had positive serologic evidence of syphilis. The incidence of congenital syphilis is especially high in cold hemoglobinuria.[42]

A small percentage of patients with late cases of syphilis show the presence of the cold hemolysin in their plasma, but only a few actually have symptoms of hemoglobinuria. Donath and Landsteiner[40] studied 93 patients with general paresis and demonstrated the cold hemolysin in the serums of 7; only 1 patient, however, had symptoms of paroxysmal hemoglobinuria. Japanese investigators[44, 45] have reported finding cold hemolysins in 20 to 25 per cent of patients with tertiary syphilis, an incidence much higher than that found by American observers. In a study of 360 patients under routine antisyphilitic therapy in an outpatient clinic, Dill[46] found only one positive Donath–Landsteiner reaction, which suggests that the probability of development of cold hemolysins may be markedly reduced by proper antisyphilitic therapy.

The fundamental abnormality existing in cold hemoglobinuria was not understood until the investigations of Donath and Landsteiner.[47] They found that when a mixture of plasma and red blood cells from a patient suffering from paroxysmal cold hemoglobinuria was chilled in ice water and subsequently warmed to 37°C., marked hemolysis occurred. The abnormality causing the hemolysis existed in the plasma rather than in the erythrocytes, since the patient's plasma was capable of hemolyzing normal red blood cells of the same blood group, but the patient's erythrocytes, mixed with normal plasma, showed no hemolysis after chilling and warming. Inactivation of the plasma complement by heat prevented the hemolysis from occurring, but the addition of fresh guinea-pig complement restored its hemolytic activity. Two phases of the reaction were demonstrated: absorption of the lysin on the erythrocytes at low temperatures, a fixation that occurred even in the absence of complement, and lysis of the sensitized erythrocytes when they were warmed, which occurred only if active complement was present.

The demonstration of this hemolysin with its characteristic properties of fixation by cold and activation by warmth in the presence of complement is known as the "Donath–Landsteiner reaction," and with the Ehrlich and Rosenbach tests it should be performed in all cases suspected of hemoglobinuria.

Since the reports of Donath and Landsteiner, there have been many investigations of the serologic mechanism of the disease. These have been summarized by Mackenzie[41] in an excellent and extensive review on cold hemoglobinuria. The cold hemolysin, although usually occurring in persons with positive Wassermann reactions, is distinct from the Wassermann reacting substances: it is possible to remove the hemolysin completely from a given serum by absorption in the cold without changing the titer of the Wassermann reacting substance. Although there is no distinct parallelism between the titers of the autohemolysin and the Wassermann reacting substance, both substances decrease in concentration in patients receiving antisyphilitic treatment. When adequate therapy of this type is administered, the clinical manifestations of the disease cease, the Wassermann reaction becomes negative, and the autohemolysin disappears from the serum in the order named. In patients who receive no antisyphilitic therapy, however, the titer of the lysin remains remarkably constant for many years. The hemolysin is extremely thermolabile and may be destroyed by the technics commonly employed for inactivation of complement.

Why an autohemolysin should develop in some patients during the course of a syphilitic infection is quite obscure. Mackenzie[41] has speculated that the lysin may be formed as an antibody response to antigens released from infected visceral organs. This speculation was provoked by the experiments of Namba,[48, 49] who was able to produce autohemolysins in syphilitic and nonsyphilitic rabbits by injecting them with emulsions of calf kidney and other organs not containing the Forssman antigen. He was able to produce hemoglobinemia in these sensitized animals by placing a rubber band around an ear and immersing it in ice water. These experiments are extremely interesting, especially in view of the fact that injections of such organ emulsions are capable of producing positive Wassermann reactions in nonsyphilitic rabbits.

Fluctuations in the titer of complement have been demonstrated in the blood of patients with cold hemoglobinuria.[44, 45, 50] After frequent attacks the complement may decrease in concentration or completely disappear, and in some cases the serum may become anticomplementary. In spite of the complete absence of complement from the patient's serum, however, severe attacks of hemoglobinuria may occur following exposure to cold.[50] In view of these facts, the Donath–Landsteiner reaction should be carried out with washed erythrocytes and with the addition of fresh complement.

The clinical features of paroxysmal cold hemoglobinemia vary widely in severity but usually follow the same general pattern. Following exposure to cold, a latent period varying from a few minutes to several hours may elapse before the prodromal symptoms of malaise, muscle aches and pains, abdominal cramps and headache appear. These symptoms are soon followed by a severe shaking chill and a rise in temperature to 102 or 103°F. The first urine voided after the chill is red or black, and subsequent specimens may be similarly colored for a few hours or several days, depending on the severity of the attack and the extensiveness of the hemolytic process. Abdominal cramps may persist for several hours but are usually of much shorter duration. They are probably produced by vascular spasm and may be relieved by intravenous injections of calcium chloride solution. The fever subsides in the course of an hour or two, and the patient then may feel slightly weak or may be prostrated, depending on the severity of the hemolysis and the degree of anemia produced. Jaundice appears within a few hours after severe attacks and may be noticeable for a day or two.

Vasomotor disturbances occur frequently during both the prodromal period and the actual hemolytic crisis. They may vary in severity from hives and mild urticaria[51] to extreme vasospasm of the type commonly seen in Raynaud's disease, with painful, cyanotic fingers, toes and ears.[45, 52] Why these symptoms of sympathetic-nervous-system abnormality should occur is quite unknown. They are not noted in other clinical types of hemoglobinemia and hemoglobinuria, and it seems probable that they are causally related to the underlying syphilitic infection.

The blood picture varies with the severity of the hemolytic process, which usually is marked enough to produce a moderate degree of anemia. Occasionally attacks may be so severe that the number of red blood cells may be reduced to 50 per cent of their pre-attack level.[40, 53] As in other types of hemolytic anemia, the bone marrow responds to the anemia with reticulocytosis and rapid blood regeneration.

Marked leukopenia develops during the course of the paroxysm, and the total white-cell count may drop to 1000 or even less[53, 54] because of the virtual disappearance of granulocytes from the peripheral blood. Similar granulocytopenia is commonly encountered in other types of hemoglobinemia and may be the result of the intravascular liberation of the breakdown products of erythrocytes.[41] Between attacks, the blood picture is normal or there is a moderate lymphocytosis.[41, 54] Thrombocytopenia of marked degree may also develop during the paroxysm.[53]

The amount of cold exposure necessary to produce the paroxysms varies markedly from patient to patient. Exposure to a temperature of 40°F. was

required to produce attacks in Macalister's[55] patients, but Strominger and Gottfried[56] reported that their patients developed symptoms if exposed to a draft from an unheated room. One of Mackenzie's[41] cases experienced spontaneous attacks while in bed in a hospital ward in the middle of the summer. Roch and Liengme[57] were able to produce paroxysms by giving their patients cold drinks.

As might be expected from the high renal threshold for hemoglobin, mild attacks of hemolysis may occur with accompanying hemoglobinemia but without hemoglobinuria.[44] Kaznelson[58] described a case with typical constitutional symptoms followed by jaundice but not by hemoglobinuria. Occasionally, hemoglobinuria may occur without constitutional symptoms.[59]

(To be continued)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31491

PRESENTATION OF CASE

First admission. A sixty-three-year-old Italian was admitted to the hospital complaining of frequency, dysuria and diminution of the urinary stream of several months' duration. He had also complained of backache for an indefinite length of time.

For several years before admission the patient had complained of epigastric pain radiating beneath the sternum and to the back. The pain was relieved by food. Melena was present on one occasion at the onset of these symptoms. He was followed in the Out Patient Department, where a gastrointestinal series revealed a questionably active old duodenal ulcer. Two months before admission, hematemesis and melena again occurred. He was treated with aluminum hydroxide and a bland diet, and his symptoms were much improved at admission.

On physical examination the patient was obese and pale. He had had chorioretinitis for more than three years and was almost completely blind. The heart and lungs were normal, except for moist rales at the right base. Rectal examination revealed a small, soft, left prostatic lobe. The right lobe was firm, and there was no clear-cut sulcus between the right lobe and the pelvic wall; the apex of the prostate was not clearly defined. The reflexes were normal.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 160 systolic, 90 diastolic.

The red-cell count of the blood was 4,500,000, with 80 per cent hemoglobin. The white-cell count was 9000, with 60 per cent neutrophils. A blood Hinton test was negative. The urine was normal. The nonprotein nitrogen was 28 mg. per 100 cc. An x-ray film of the chest was negative. The heart shadow was a little prominent in the region of the left ventricle. An intravenous pyelogram revealed small kidneys and normal function.

A transurethral resection was done, and microscopic examination of the fragments showed benign hyperplasia; there was no evidence of malignancy. The patient recovered uneventfully and was discharged improved.

*On leave of absence.

Second admission (two years later). The patient was followed in the Out Patient Department. The right lobe of the prostate remained firm for about a year but did not increase in size. He complained of anginal pain and exertional dyspnea. The cardiac rhythm was regular. An electrocardiogram showed slight left-axis deviation. A QRS complex was notched, and R_4 and T_4 were low. For ten months prior to readmission the induration of the right lobe of the prostate seemed to spread into the left lobe. He was readmitted to the hospital for further study.

Except for the prostatic induration, physical examination was negative. An x-ray film of the chest showed no evidence of metastases. The serum calcium was 10.8 mg. per 100 cc., the phosphorus 2.5. The acid phosphatase was 3.3 units per 100 cc., and the alkaline phosphatase 3 units. Believing that the prostate was carcinomatous a bilateral orchidectomy was performed, following which the patient was discharged in good condition, with instructions to take 1 mg. of stilbestrol twice daily.

Final admission (two and a half years later). The patient was again followed in the Out Patient Department, where one month after discharge the right lobe of the prostate was found to be markedly reduced in size but still extremely firm. The left lobe was soft. Stilbestrol was discontinued. Ten months later he complained of vague, transitory pain in the neck and back. Stilbestrol was again prescribed; the symptoms were relieved, and his general condition improved. Six months before readmission, however, he complained of pain in the right hip posteriorly. X-ray studies of the lumbar spine and pelvis showed no evidence of metastases. Two months before readmission, while turning on his left side in bed, he suddenly experienced sharp pain over the left chest, radiating to the left arm and later to the left leg. The pain persisted, with exacerbations, and was not relieved by the ingestion of food. There was no change in the character or color of the stools. For a month before readmission he vomited after almost every meal. Severe dyspnea was also present. He had lost no weight. He was again referred to the hospital.

Physical examination showed an obese, pale, and dyspneic man with grunting respirations. The chest was emphysematous, with numerous fine rales. The heart was negative. The abdomen was prominent, with no evidence of fluid. The liver was palpable three fingerbreadths below the costal margin; it was tender. There was no edema. The prostate was irregular but not hard.

The urine was normal. The red-cell count was 2,500,000, with 6.5 gm. of hemoglobin. The white-cell count was 4900, with 44 per cent neutrophils. Three stool examinations were guaiac positive. The nonprotein nitrogen was 52 mg. per 100 cc., falling later to 30 mg. The acid phosphatase was

3.6 units. The gastric juice contained 15 units of free acid in a fasting specimen and 90 units after histamine stimulation.

X-ray examination of the chest showed diffuse nodular and linear density throughout both lung fields, slightly more marked on the left than on the right, extending toward the periphery. There were shadows suggestive of enlarged nodes at each hilus. The heart was normal. The diaphragm was low but showed fairly good respiratory motion. A gastrointestinal series revealed a wide esophagus, without definite varices. The stomach showed thickening of the mucosal folds and considerable narrowing of the antrum and prepyloric areas. A definite crater could not be demonstrated, although one plate showed a shadow suggestive of a crater at the angle. No peristalsis was seen along the greater-curvature margin of the area of narrowing. The duodenal cap was deformed, and in the narrowest portion there was a crater approximately 4 mm. in diameter. The remainder of the duodenal loop was not remarkable. A barium enema revealed filling of the entire colon. The terminal ileum could not be filled, despite positioning and pressure. There was an area of narrowing in the sigmoid, not completely visualized because of gas in this area. Gastroscopy was negative.

The day after admission the patient vomited about 400 cc. of cloudy, yellow, guaiac-positive fluid. He also complained of abdominal discomfort and gas. On the ninth day a peritoneoscopy revealed a hob-nailed liver, and biopsy showed mild portal cirrhosis. Three weeks after admission he complained of pain in the left side of his body, including the chest, abdomen and leg. The abdomen was markedly distended, and a fluid wave was present. Peristalsis was normal. There was tenderness to pressure over the transverse colon. There was no tenderness of the calf muscles. A cecostomy was performed.

Although the cecostomy drained well, abdominal distention persisted and the patient became apprehensive and disoriented. Dry, fine, crackling, inspiratory rales were heard at the left base, with dullness in the same area. An x-ray film of the chest was unchanged. Upper abdominal pain was present. A flat plate of the abdomen showed marked distention of the entire colon down to the lower sigmoid, with no air in the rectum. There was no evidence of small-bowel distention.

On the thirty-third hospital day an exploratory laparotomy was performed. The liver was cirrhotic, and there was a small amount of ascitic fluid. No neoplasm could be found in the bowel. There were extensive inflammatory adhesions around the sigmoid, but no evidence of obstruction. No diverticulitis was observed. After the operation the patient had labored respirations and expired on the second postoperative day.

Differential Diagnosis

Dr. Wyman Richardson: Epigastric pain radiating to the sternum and to the back is not inconsistent with the pain of duodenal ulcer, usually one on the posterior wall I should say.

I shall point out that an x-ray examination of the chest was negative, not only four years before admission but also two years later. The patient complained of anginal pain and exertional dyspnea. It is usually true that people with anginal pain do not complain of exertional dyspnea. Exertional pain would be anginal. I do not know whether or not we should pay much attention to the dyspnea. You will note that the serum calcium and phosphorus were normal, also the phosphatase. There was no evidence of osteoblastic activity, nor was there evidence of metastases from a carcinomatous prostate.

We then come to the time when the patient turned over on the left side and had the sharp pain. To me, that usually means a fracture and usually a pathologic fracture. The problem here is, Why does he have a fracture that gave him pain in the chest and in the arm and later in the leg? I cannot think of any one fracture that would do it. All these seem to have happened at about the same time. I should imagine that a fracture would have to be in the cervical region to produce pain in the arm. It should be a high upper dorsal vertebra or rib to produce pain in the chest, but by no means can I explain pain in the leg. One could explain pain in the chest radiating down the arm, followed later by pain in the leg, by a pulmonary embolus and later a thrombophlebitis in the leg. We shall have to consider that more seriously later. The degree of pain is not entirely clear, but it persisted with exacerbations and was not relieved by the ingestion of food. I do not imagine that the pain in the leg was due to ulcer, and probably not the pain in the chest, assuming that he had an ulcer.

The next thing to comment about is the large liver, which was three fingerbreadths below the costal margin. It may or may not have been a large liver, depending on the upper border of dullness. I am not going to be fussy and ask for that. One would not expect the patient to have a large liver from the peritoneoscopic findings.

Is there any record of the temperature at the final admission?

Dr. Ronald C. Sniffen: Here is the chart.

Dr. Richardson: It is a relatively flat temperature curve, with occasional spikes above 100°F. by rectum, on one occasion reaching 101°. It does not suggest sepsis.

There was a lot of free hydrochloric acid after histamine. The stomach contained a large amount of fluid, 400 cc., and the fluid was yellow, which suggests that it contained bile and therefore indicates that there was not complete pyloric obstruction.

Let us see some of the x-ray films, Dr. Hale. I am especially interested in the chest. Also, I wonder if there is any film that shows the upper dorsal or cervical vertebras.

Dr. Clayton H. Hale: This chest film, taken four years before the final admission, is reported as essentially negative, and I agree with that interpretation. This film was taken two years later and is also essentially negative except that there is a slight suggestion of enlargement of the left hilus. This third film was made this year and shows a large round shadow overlying the left hilus. This next film was taken about a month later, and because a portable machine was used it is difficult for me to be sure of any great change in the pulmonary vessels since the earlier examination. You will notice, however, that the left half of the diaphragm is high and that the hilar mass is more noticeable than it is on the previous film. It is completely covered by the heart shadow, but I am quite sure that it is an enlarged node in the left hilus.

Dr. Richardson: I thought you were going to say something about the linear shadows.

Dr. Hale: I think the difference is explained by the fact that it was taken with a portable machine.

Dr. Richardson: Can you see any bone lesions?

Dr. Hale: I do not see any abnormality in the ribs; no metastases are demonstrable.

Dr. Richardson: There is no osteoblastic activity?

Dr. Hale: No. There is a deformed duodenal cap, with a crater in the central portion on the posterior wall. None of the films show the descending loop particularly well. I shall have to say that there is nothing definitely abnormal in the region of the ampulla; it is not too well demonstrated, however. The folds of the stomach look large in these films, but except for the possibility of retained secretions in the stomach at the time of examination, I should have to call the stomach normal. I cannot make out any areas of ulceration, nor can I see any evidence of rigidity of the wall.

Dr. Richardson: Do you see any linear markings in the lungs that look like healed infarcts?

Dr. Hale: No.

Dr. Richardson: We have to explain why this man died. I do not believe that he had carcinoma of the prostate or that his prostate had anything to do with the terminal illness. We know that he was an Italian, and we have definite evidence that he had portal cirrhosis of the liver. We also have definite evidence that he had duodenal ulcer, and the combination of peptic ulcer and portal cirrhosis is not too unusual. Also portal cirrhosis in Italians, as I have pointed out many times, is frequently seen. The question is, Did this man have anything else besides that, or did he die as a result of surgical procedures that perhaps were not indicated? Morphine given preoperatively and postoperatively in a patient with cirrhosis of the liver is dangerous. This man might also have had too many transfusions. My guess is that that is why he died, but I have not at hand the postoperative orders and I do not know whether he received morphine. If he did not, I am all wrong. You all know that in a patient with a sick liver any drug is likely to be dangerous, especially morphine. We have had several extremely disturbing results following the administration of morphine to patients with sick livers.

He may have had some other disease. He apparently did not have an infection. I see no evidence of miliary tuberculosis or anything of that sort, so that I should rather not mention infection. That brings us to tumor. If he had tumor, what sort of tumor was it? We have no evidence to help settle this question. He had an anemia, — a red-cell count of 2,500,000, — only slightly hypochromic by measurement. Of course, if I had a blood smear and a microscope I should not be in this difficulty! One can usually tell from a smear whether one is dealing with infection, tumor or blood loss. This man had apparent liver failure, however; he had also been known to bleed and had been vomiting. All these things can contribute to anemia of this degree. One cannot say that the anemia was not due to tumor involving a large part of the bone marrow, which can occur with negative x-ray films. One always has to think of lymphoma. There is nothing more to suggest it. I thought of lymphoma because of the x-ray report in the protocol, but the interpretation of the films that Dr. Hale has just shown makes it seem unlikely. I suppose a lymph node in this region could be due to a lymphoma as well as to anything else, but it does not suggest it to me. Does it to you, Dr. Hale?

Dr. Hale: No.

Dr. Richardson: One might think of bronchiogenic carcinoma, with an enlarged lymph node, or of some other type of metastatic node.

We all know that hepatoma occurs in the presence of cirrhosis of the liver and only then. I say that, but I believe that we had one case without cirrhosis of the liver. Do you remember that, Dr. Sniffen?

Dr. Sniffen: Yes; we have had one.

Dr. Richardson: In general, hepatoma occurs in the presence of cirrhosis of the liver. One has to consider hepatoma in this case. I see no way to rule it out or in. The whole thing comes down to the question, Did this man have a malignant tumor? How do we account for the pain, which I emphasized in the first place? I was going to say, and very likely I am going to stick to it, that it was not due to fracture, which it sounds like, when he turned over in bed and had a sharp pain, but rather to a sudden embolus and that he later on had pain in the calf of his leg from thrombophlebitis. I thought that I should see plenty of evidence of disease in the x-ray film of the chest, with old pulmonary infarcts, but I do not see anything there.

I have here a long list of symptoms that I was going to try to explain, but I have talked enough. We have evidence that he had angina, and I believe some coronary sclerosis, but it does not seem to me probable that that was the cause of death or enters very much into the clinical picture. The dilatation of the bowel could perfectly well go with a sick liver in a malnourished man. It is frequently seen in pernicious anemia and in any nutritional disturbance. I do not believe that we have to postulate obstruction. A cecostomy was done and no obstruction demonstrated, as I understand it.

I am going to say that this man, besides having benign hypertrophy of the prostate, which is more or less historical, and a mild coronary sclerosis, had portal cirrhosis of the liver and peptic ulcer involving the duodenum and perhaps the stomach, and that he had nothing else. I think that perhaps he died a postoperative death for the reasons outlined.

Dr. J. H. Means: I saw this man during the first part of his last admission; I did not witness the terminal events, because the service changed. We went through much the same diagnostic throes that Dr. Richardson has. We were quite impressed by the fact that he had been orchidectomized and treated by stilbestrol. We could not be sure that there was any evidence that he had ever had carcinoma of the prostate. We also thought that the prostate had nothing to do with the picture. He was bleeding from the gastrointestinal tract and apparently had a large liver. I was not certain of the latter, but I think that the others who saw him were. I toyed with the idea of cancer of the stomach, perhaps with involvement of the liver, but I do not believe that the others were impressed with that possibility. At the time I left the service we established the diagnosis that he did have cirrhosis but it was described as an early one. I was not convinced that that was the only thing he had. He had an ulcer, and I thought that he might have a cancer as well.

Dr. Richardson: There is one other thing that I ought to mention. There has been some talk to the effect that stilbestrol is toxic to the liver. I believe that that has been disproved.

Dr. Fletcher H. Colby: I have not seen any evidence of toxicity when the drug has been given in large amounts for a long period of time.

I saw this man five years after his transurethral resection and three years after the orchidectomy. At that time, there was no evidence that he had cancer of the prostate. As we read over the history, we find that he had a transurethral removal of prostatic tissue, which had been examined and reported benign. That is not an infrequent occurrence in people who do have cancer of the prostate, because the most frequent place for cancer of the prostate is in the posterior lobe. In transurethral resection or subtotal prostatectomy, we do not remove any of the tissue from the posterior lobe. So it is possible that he had cancer of the prostate limited to the posterior lobe of his gland. It is also a frequent occurrence in patients with cancer of the prostate who have had an orchidectomy performed that the regression of the tumor is so marked that on clinical examination no one can be certain whether the patient has cancer of the prostate. It is true that the regression is, in our experience, only temporary, lasting for a period of a few years. This man lived for three years after the orchidectomy and it still is possible that he had cancer of the prostate. He had also been treated with stilbestrol which causes regression of the primary tumor. I do not believe that anyone can say from the evidence presented in this history and examination whether or not the patient had cancer of the prostate.

Dr. Earl Glendy: To go back to the symptomatology, in the presence of pain in the chest that later radiated into the extremities, one should always think of some vascular accident, such as a dissecting aneurysm; but that usually occurs in persons with considerable evidence of hypertension. There is only one record of the blood pressure given in the protocol. Apparently little attention was paid to the blood pressure and the patient's cardiovascular status after the episode of pain in the chest and leg, so that I doubt that a dissecting aneurysm was present. It is another thing, however, that one should think of with pain radiating to the chest and to the lower extremities.

Dr. Richardson: It is fair to say that I thought of dissecting aneurysm and ruled it out particularly because the cases I know of, with dissection down to the iliac vessels, have had midback pain.

Dr. Glendy: The radiation of the pain is bizarre, but the pain usually does not radiate into the arm, which is another point against a dissecting aneurysm.

Dr. Richardson: I meant to add one other thing. I have to put a question mark after the thrombophlebitis, which I have already mentioned, and I should also like to add pulmonary infarcts. I shall probably wish that I had not.

Dr. Wade Volwiler: I should like to say something in defense of the initial surgery. During one afternoon on the ward, this man began to complain of violent cramplike abdominal pain, and the previously distended abdomen became more distended and the normal peristalsis became high-pitched and quite typical of intestinal obstruction. He was taken to the X-ray Department, where a flat abdominal film demonstrated large dilated loops of colon, including the ascending, the transverse and part of the descending colon, stopping abruptly in the sigmoid, which was compatible with obstruction of the sigmoid. On the basis of that, the original cecostomy was done. Unfortunately after the bowel was decompressed a barium enema was not done before the final surgical maneuver was carried out.

Dr. Richardson: I was not objecting to the

cecostomy, but I see no reason for the laparotomy except plain curiosity. I do not believe that it was justified.

DR. VOLWILER: Certainly not without further x-ray evidence.

CLINICAL DIAGNOSES

Carcinoma of sigmoid.
Portal cirrhosis of liver.
Duodenal ulcer.

DR. RICHARDSON'S DIAGNOSES

Portal cirrhosis of liver.
Peptic ulcer of duodenum and possibly stomach.
Coronary sclerosis, mild.
Thrombophlebitis, with pulmonary infarcts?
Prostatic hyperplasia.

ANATOMICAL DIAGNOSES

Oat-cell carcinoma of lung, with metastases to regional lymph nodes, liver and cystic duct lymph nodes.
Portal cirrhosis of liver.
Chronic myocarditis, nonspecific.

PATHOLOGICAL DISCUSSION

DR. SNIFFEN: This patient was obese, with female hair distribution. We could not find a cause for the apparent intestinal obstruction. The stomach contained a 4-mm. benign, peptic ulcer on the lesser curvature, 10 cm. proximal to the pyloric ring. The prostate was small and did not contain cancer. The liver weighed over 2000 gm. and had the gross and histologic appearance of portal cirrhosis. In addition, the parenchyma was studded with many 2- to 10-mm. nodules of metastatic cancer, and a large lymph node containing metastatic carcinoma almost occluded the cystic duct.

The primary tumor was found in the left lung. It was only 1.5 cm. in diameter and arose in the dorsal division of the lower lobe bronchus. Several satellite nodules of the same size were grouped around this tumor, which proved to be an oat-cell carcinoma. The hilar lymph nodes were not involved. The patient's heart was of normal weight, and there was disease in the coronary arteries. The myocardium, however, showed a patchy chronic myocarditis. The character of the inflammation was not specific, but it included giant cells. I should not consider this to be an important factor in the patient's death.

DR. RICHARDSON: What about the bone marrow?

DR. SNIFFEN: There were no metastases in the vertebral marrow.

DR. RICHARDSON: Why did he have pain in the left arm and so forth?

DR. SNIFFEN: I cannot explain that. We did not examine the veins of the extremities or the long bones.

DR. RICHARDSON: Then I still have a loophole.

DR. SNIFFEN: This is one of the few cases we have seen of metastatic carcinoma in a cirrhotic liver. Reports vary concerning the frequency of its occurrence, some stating that it is rare, the cirrhosis protecting the liver from metastases, and others that the incidence is the same in both the cirrhotic and the noncirrhotic liver.

CASE 31492

PRESENTATION OF CASE

A forty-two-year-old man was admitted to the hospital complaining of paralysis of the left arm and leg.

Three weeks before admission he noted the onset of "tightness" in the neck and "light-headedness" without definite headache. These symptoms became more marked. Five days before admission he awoke complaining of weakness and numbness of the left hand and arm, which later in the day was followed by slight numbness and heaviness of the left leg. The numbness was described as a cold, dead feeling without tingling. On the evening of the same day he had a single generalized convulsion. The left hemiparesis progressed, and three days before admission the patient could not walk because of marked weakness of the left leg. The following day he was unable to move either the left arm or the left leg. Left facial weakness and ptosis appeared. At about the same time slowing of the mental processes was noted, and during the two days before admission he became increasingly lethargic. He never complained of nausea, vomiting, headache or visual or auditory disturbances. There was no history of head injury.

For a number of years he had had a slight cough, productive during the year before admission of a small amount of mucoid sputum. There was no hemoptysis, chest pain or weight loss.

Physical examination revealed the patient to be lethargic but oriented; at times he was comatose. The fundi were normal. The neck was slightly rigid. The lungs were dull to percussion throughout. The breath sounds were diminished over the entire right chest; those signs were most marked at the bases, where coarse rales were heard. The heart was slightly enlarged to percussion. The rhythm was regular except for an occasional extrasystole. The abdomen was moderately distended. There was a left homonymous hemianopsia. There was a left hemiplegia; the upper as well as the lower facial muscles were paralyzed, and the arm and leg were flaccid except for slight spasticity of the biceps. Sensation was impaired over the left half of the body; touch was not felt, pinprick was barely perceptible, and proprioceptive sense was lost. The arm, knee and ankle jerks were active, more so on the left than on the right. The plantar reflex was extensor on the left, and normal on the right.

Examination of the blood revealed a red-cell count of 5,080,000, with 14 gm. of hemoglobin, and a white-cell count of 16,100, with 90 per cent neutrophils, many of which were band forms. The urine was normal. Lumbar puncture yielded clear, colorless fluid under an initial pressure equivalent to 310 mm. of water. The cell count was 5 lymphocytes and 4 large mononuclears; no red cells were seen. The total spinal fluid protein was 46 mg. per 100 cc., the sugar 116 mg. The gold-sol curve was 0011223110. Cultures of the fluid were negative.

An x-ray film of the chest showed a high diaphragm, but no evidence of pulmonary or cardiac disease. The skull, mastoid processes and sinuses were normal.

Shortly after admission, the patient sank into a deep coma. The right pupil, and later the left, became dilated and fixed to light. A craniotomy was done. The patient died six hours later or eleven hours after entry. The temperature had risen to 105.3°F., the pulse to 100, and the respirations to 60.

Differential Diagnosis

Dr. Avery D. Weisman: In reviewing this case I should say that the sensory involvement ought to be considered in connection with the fact that the man was not alert. He was stuporous and at times comatose.

I think that this man's chest findings were probably due to pulmonary edema, with perhaps atelectasis.

Among the things that we do not have available in attempting to solve this problem of differential diagnosis are: the temperature on entry, the blood pressure, the extraocular movements, the reaction of the pupils to light and the serologic findings.

Primarily one ought to consider an extracerebral lesion — subdural hematoma, for example. There was no history of head injury, but a good many people with subdural hematoma come into the hospital without such a history or the head injury is minor. Against subdural hematoma, however, is the absence of headache. Headache, especially unilateral headache, is often a symptom in subdural hematoma. Another point against it is that the hemiparesis appeared several days before the disturbance of consciousness. In most cases of subdural hematoma the reverse is true. The patient begins to get drowsy and toward the end develops weakness of the arm and leg. Another point against subdural hematoma is the complete left hemiplegia. When patients with subdural hematoma develop hemiparesis it is usually relatively mild. Still another point against it is the hemianopsia. I realize, however, that in a small percentage of cases of hematoma, hemianopsia is said to be present, but the figure is well under 5 per cent. When it is present, one wonders whether there is also an involvement of the posterior cerebral artery. I believe that subdural hematoma is the only significant extracerebral lesion that one should consider, but I do not believe that that is what he had.

Thus we must think of some intracerebral lesion that can give this sort of picture. The first thing that comes to mind is a rapidly developing tumor, such as a metastatic tumor or, likelier, a glioblastoma, which as you know can sometimes appear so abruptly that it almost simulates a vascular accident. But it seems to me that the symptoms that this man presented were too widespread and too rapid — that is, the complete paralysis and the hemianopsia came on in too short a time — to be consistent with a brain tumor. In other words, this man within a few days developed weakness, severe paralysis of the arm, leg and face and also hemianopsia, and it is difficult to conceive of a glioblastoma, even one of the most malignant type, that would give this picture in such a short time. Furthermore, I should think that, were this the case, headaches would have been a more prominent part of the clinical picture.

One might also consider, among other intracerebral lesions, brain abscess. I might dispose of this possibility briefly by saying, first, that we have no idea where the abscess could have arisen and, second, that the course was too rapid even for an acute brain abscess. The acute brain abscesses that I have seen have all had a course of at least ten days. Also, if an abscess followed such a rapid course, one should have found more evidence of spinal-fluid abnormality on lumbar puncture.

We then come to other conditions, which seem likelier. The first one is central-nervous-system syphilis, because we know that neurosyphilis can often give paralysis and also a convulsion, which we note that this man had. But what kind of neurosyphilis could he have had? The most obvious one that comes to mind is general paresis, because that can occasionally produce a picture like this. I think, however, that the picture is exceedingly acute even for the most malignant type of general paresis. Furthermore, the spinal fluid should have been more abnormal than it was. The spinal-fluid protein was just on the borderline, as was the gold-sol curve and the cell count. Also, the pressure was elevated, which is not often seen in general paresis. It is seen, however, in syphilitic hydrocephalus; but that is an extremely rare condition. We do not know the serologic findings, which would tell us whether the patient had syphilis of the nervous system. As I have said before, we should like to know whether his eyes reacted to light, but even without that information I do not believe that this man had paresis. The other form of neurosyphilis to be considered is the meningovascular type. We know that that can often lead to situations that simulate or actually are vascular lesions. Again, in a man who ran such a rapidly lethal course I should expect more abnormalities than those which the lumbar puncture showed.

There are only two other significant vascular lesions that I want to consider — thrombosis and hemorrhage. Let us consider hemorrhage first. From the rapid course that this man followed and from the extensiveness of the lesions that he presented, it would seem that, if this were solely due to hemorrhage, one would have found red cells in the spinal fluid. Besides, the course was too long for hemorrhage, particularly for a large hemorrhage, which it would have to be in order to produce this picture. Cerebral hemorrhage usually comes on and ends in a much more abrupt manner. So that leaves me with just one other diagnosis, namely, thrombosis. This too, is usually a much more abrupt lesion. Furthermore, it is not ordinarily associated with convulsions. Convulsions and a relatively slow course are not unheard of, however, and if one had involvement of small arteries first and then large ones, it could produce this kind of clinical picture. Furthermore, when thrombosis does come slowly, one is apt to observe convulsions. When convulsions do occur in association with thrombosis, and it is not a rare phenomenon, they seem to come most frequently with occlusion of the middle cerebral artery.

In regard to localization, we know that a somewhat similar picture to this — that is, hemiparesis, hemianopsia and hemihyperesthesia — can be produced by thrombosis of the anterior choroidal artery. In such cases, however, weakness is not so pronounced; it is usually mild. Also little or no disturbance of consciousness is found. The ptosis noted in this case, I believe, was not associated with any involvement of the oculomotor nerve, such as in Weber's syndrome, but probably was due to weakness of the frontalis muscle. Therefore, I think that the lesion in this case was supratentorial, in the right cerebral hemisphere and probably in the distribution of the right cerebral artery. The pathologic process was probably thrombosis.

Dr. Charles S. Kubik: The pupils reacted normally when the patient was admitted. The rectal temperature was 100°F., and the blood pressure 120.

Dr. Porter, have you anything to add?

Dr. Huntington Porter: The only thing I should like to say is that I thought the sensory findings were dependable, since one could demonstrate good position sense and pain sense on the right side.

Dr. William H. Sweet: The findings at operation were rather interesting. An enormous bone flap over the central region was turned down, disclosing a dura under extreme tension. I did not believe, as Dr. Weisman did, that a rapidly growing tumor or an abscess could be ruled out positively on the basis of the clinical course. I thought that perhaps the most hopeful thing would be that he had a slowly developing hemorrhage into a more or less benign tumor. At any rate it was with the hope of finding something of that sort that a craniotomy was carried out.

When the dura was reflected over the temporal lobe, grossly abnormal gyri were seen, and a ventricular puncture needle put into this portion of the temporal lobe fell through the substance of the brain by its own weight, indicating a gross area of softening. On direct inspection, we thought there might have been an area of diffuse cerebritis or an area of softening with vascular occlusion. The temporal lobe was removed in an attempt to remove the tentorial pressure cone.

Dr. Augustus Rose: Would not the dilatation of the pupils and the coma suggest a pressure cone as the final cause of death?

Dr. Weisman: Yes.

Dr. Kubik: You have in mind a temporal pressure cone as a cause of the dilatation of the right pupil?

Dr. Rose: Yes.

Clinical Diagnosis

Brain tumor.

Dr. Weisman's Diagnoses

Occlusion of right middle cerebral artery, probably due to thrombosis.
Cerebral infarction.

Anatomical Diagnoses

Embolism of middle cerebral artery, right.
Cerebral infarction.

Pathological Discussion

Dr. Kubik: This was a difficult and puzzling case. It is unusual in cerebral infarction for the symptoms to progress gradually over so long a time or to have such a marked elevation of spinal-fluid pressure. Such pronounced coma as this patient eventually had, before he was operated on, is not frequent. Yet, the autopsy confirmed Dr. Weisman's diagnosis.

There was an occlusion of the right middle cerebral artery, and softening of a large part of the right cerebral hemisphere. The vessel was occluded by an embolus, not by a thrombus, but no source for the embolus was found. There was some infiltration of the embolus with polymorphonuclear cells, which suggests an infectious process, and perhaps the possibility of an undiscovered or overlooked subacute bacterial endocarditis has to be considered. There were no infarcts in any of the other organs. There was a terminal bronchopneumonia. Examination of the lungs microscopically did not reveal any thrombosed lung veins, as a possible source of emboli.

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OUT OF THE (GIFT) HORSE'S MOUTH

There is, in the drug detailing game, no particular time of year when the Christmas spirit seems especially appropriate; the wise men bearing gifts may appear at any season, on any working day and at any hour of the day, if the doctor is in. If they can buttonhole him for an impressive conference so much the better; if not, there appears upon the waiting-room table or the laboratory shelf the latest literature on the newest nose drop, vitamin combination, chemotherapeutic agent, antibiotic or what have you, with samples, frequently in quantity, despite the well known theory that the gift without the giver is bare.

One inference to be deduced is that the competition among drug manufacturers is too hot to handle, and another that the bags of the detail brigade are too heavy for the representatives of this friendly tribe to tote too long from door to door. In any event the situation poses a problem for the scrupulous physician in our frugal New England states, who is hard put to give away, as fast as they come in, those samples that his family cannot personally use. Being of New England stock, he hesitates to pitch out the unwanted bottles and boxes until he is sure that their contents are absolutely worthless; and being scrupulous, he cannot bring himself to sell those that might have value. And so his shelves grow fuller and fuller, to hastening pills a prey, as Dr. Goldsmith might have put it.

Advertising, we have been led to believe by the advertising fraternity, is good business, and so it must be, particularly in our amazing form of society where it is necessary to convince the public that it must have something that it has never heard of and has always done perfectly well without, in order that the wheels of industry may hum and that other workers, in turn, may earn the wherewithal to purchase similar products. It is difficult, nevertheless, to determine just what forms of advertising bear the best fruits, and it seems likely that the wholesale sowing of unsolicited drug samples must increase, to the ultimate consumer, the cost of these goods to an unwarrantable degree. A solicited sample is one thing: the advertising of it has been so well conceived or the product is of such potential merit that the solicitor's interest has been aroused and he takes the trouble to return the postcard. On the other hand, the stream of unsolicited samples that pours into the practitioner's office does little more, often, than to arouse in the doctor a feeling of frustration at his hopeless efforts to achieve and maintain any degree of orderliness.

Some astute aphorist at one time enunciated the doctrine that we get, in the main, what we pay for. This maxim was intended to give point to a general rule, with all its exceptions, not simply to declare a natural law that must remain immutable under all circumstances, like Boyle's law or the law of gravity or even, perhaps, the law of averages. Despite the

many possible exceptions to the rule, the lavish sampler might at least turn it over in his mind.

DIABETIC NEUROPATHY

The article on diabetic neuropathy by the late Dr. Abraham Rudy, published elsewhere in this issue of the *Journal*, deserves careful scrutiny. If his observations are properly interpreted and intelligently applied, many a diabetic man and woman will be lifted out of the "Slough of Despond," usually considered to be brought about by arteriosclerosis and old age, to a level where they can be studied, where their neuritis can be diagnosed and where their bodies can be rescued with good diabetic care.

Certain implications might be ascribed by the nonreflective reader to Dr. Rudy's descriptions of a group of patients in whom the neuritis appeared to follow the inauguration of treatment. In several, it is true, the neuritis did come to light when treatment was begun, but careful reading of the text leads one to suspect that the neuropathy was present in latent form long before it was recognized by the patient or the physician. Indeed, one must concede that the symptoms and signs of diabetic neuropathy rarely develop following the beginning of diabetic treatment. Rundles[1] discusses this very point in a recent paper on diabetic neuropathy, stating that in only 16 per cent of 125 cases of diabetic neuropathy were symptoms of neuritis first noticed within two weeks after treatment was commenced. Diabetic neuropathy as a rule does not develop or progress when the diabetes is well controlled; in fact just the opposite is true. The term "well controlled," however, is not always properly employed. One is not justified in stating that a diabetic patient is well controlled if the urine is sugar free, and the blood sugar normal — altogether too many patients of that type were seen in the days of undernutrition, and certain of them died. Control of diabetes mean- normal chemical tests along with mental and physis cal vigor and a reasonable body weight. These reflections, however, do not detract from Dr. Rudy's paper, and hereafter the physician must look not alone for cancer and arteriosclerosis in every patient with diabetes whom he sees but also for symptoms, premonitory or existing, of neuropathy.

Rundles emphasizes that the increase of the total protein of the spinal fluid often observed in cases of diabetic neuropathy[2-4] is an aid in differential diagnosis. On the other hand, some patients with severe diabetic neuropathy have a normal spinal fluid.

Important from the patient's point of view are the pathetic histories recounted by Dr. Rudy. Months are usually required for recovery — a halting, painful progress back to health. Mental and sensory improvement often occurs earlier than does physical improvement. Indeed, one can almost safely say that the neuropathic patient will finally get well if he lives long enough: there is no royal road to recovery.

Dr. Rudy has stated that there is "no direct relation between the duration or the severity of the diabetes and the presence of the neuropathy." It might be added that the development of neuritis in a case of mild and well treated diabetes of short duration is so unusual and spectacular that it always attracts more attention than it deserves. Rundles writes:

> Insofar as diabetic retinopathy and diabetic neuropathy coincide I have found an identical background of inadequate care extending over a considerable length of time preceding each complication. . . . It will be apparent that few of our diabetics who developed neuropathy had received treatment meeting even these minimal standards and that the period of neglect had extended over a period of many months or years. None of this group . . . [were] found to be among those regularly attending our diabetic

MASSACHUSETTS MEDICAL SOCIETY POSTWAR LOAN FUND

The Postwar Loan Fund has been set up, and all discharged medical officers who were members of the Massachusetts Medical Society in good standing at the time of their entry into the service may apply for loans from this fund. For further information apply to:

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Postwar Loan Fund
8 Fenway
Boston 15, Massachusetts

clinic or under the adequate supervision of competent physicians with provision made for enlightened dietary management, frequent urinalyses, blood sugar determinations, when indicated, and checkup visits. In 25 cases there had been no diabetic treatment at all before the hospital admission. Of the remaining patients that had had some treatment, nearly every one (98 cases) had had what could be called "poor" care partly because of the obvious likelihood of failure.

Studies on the vitamin content of the diets of diabetic patients with and without neuropathy give little encouragement to the assumption that avitaminosis is the primary cause of this diabetic complication. In general it can be said that, if a true vitamin deficiency exists, a definite response should follow two weeks of adequate vitamin therapy. Deficiency states, however, are often so difficult to recognize that it is probably wise to give liberal doses of the various vitamins, including thiamine chloride, along with other therapeutic measures. Meanwhile, one should remember that this type of therapy is probably the least important of all the things that are done to bring the diabetes under control and that one must wait for the diabetic neuritis to disappear.

Although two of the late complications of diabetes, arteriosclerosis and diabetic cataracts, are irreversible once they become established, the early stages of diabetic neuropathy and of retinopathy are far more susceptible to treatment if it is carried on so rigorously that both the chemical and physical conditions of the patient are kept close to normal. Dr. Rudy's paper shows that even extreme cases of diabetic neuritis can be helped. This distressing complication can undoubtedly be cured in mild cases and can be averted in the majority of diabetic patients by prophylactic therapy.

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OBITUARY

HUGH CABOT
1872–1945

Hugh Cabot died a few days after his seventy-third birthday from a coronary attack, which was immediately fatal.

He was born in Beverly, Massachusetts, on August 11, 1872, one of seven brothers. He prepared for college at Roxbury Latin School and graduated from Harvard College in 1894. Four years later he graduated *cum laude* from Harvard Medical School, having stood second in his class. After completing his surgical internship at the Massachusetts General Hospital he began the private practice of surgery in Boston, at first as assistant to his uncle, Dr. Arthur Tracy Cabot.

His progress up the professional ladder at the Massachusetts General Hospital and at the Harvard Medical School was what would be expected. At the one he served consecutively as instructor, assistant professor and professor, and at the other, as out-patient surgeon, assistant surgeon and surgeon. His interest in urologic surgery was stimulated by that which his uncle had always taken in this branch, and largely because of this stimulus he organized the Department of Genitourinary Surgery at the Massachusetts General Hospital in 1910, with a clinic in the Out Patient Department and ten beds in the hospital.

In 1916 he went to France as head of the Harvard Unit, serving through the last of the war as a lieutenant colonel in the British Expeditionary Force in charge of Base Hospital No. 22.

Shortly after his return in 1920 he went to Ann Arbor as professor of surgery at the University of Michigan Medical School, and two years later he became dean. In 1930 he left Ann Arbor and went to Rochester, Minnesota, where he became a consultant and operating surgeon at the Mayo Clinic and professor of surgery at the Graduate School of the University of Minnesota Medical School. He held these positions until his retirement in 1938.

He married Mary Anderson Boit in September, 1902. She died at Rochester, Minnesota, in October, 1936. They had four children — three sons and a daughter. In October, 1938, he married Elizabeth Cole Amory. She and the three sons survive.

So much for the skeleton that gives only the framework of his life. What about the man? Three lines at the head of his Fiftieth Anniversary College Report may start the picture: "Eminent Surgeon and Medical Dean. Eloquent Speaker and Writer. Ardent Crusader in War and Peace, Brushing aside All Men and Things if They Block the Way to Truth."

Very early he became interested in the out-of-doors, first through his father, who was an excellent naturalist. With him he spent much time in the fields and woods in Brookline. When only thirteen he went with a guide into the Adirondacks. Three years later he was it the Maine woods, then to New Brunswick, Quebec, Labrador, British Columbia and Alaska. For many years the vacation he loved best was to pick out some unmapped spot in the North Country with Tommy, his Indian guide, and to spend several weeks exploring. Dur-

ing these extensive trips, with their whole equipment on their backs, he learned to live off the country. Because he had to meet all conditions of weather and travel without any of the artificial aids of civilization, he early learned that to live in any kind of comfort, in fact often even to live at all, it was essential to know and follow the laws of Nature. This was still further emphasized in his sailing days, for he was an ardent yachtsman. He not only cruised the New England coast himself but sailed as a Gloucester fisherman to the Grand Banks with Tommy Bohlin, in the days when all dependence was on sail and the first boat in to the market with fish got the money. It is perhaps from these out-of-door contacts that he gained his uncanny ability to foretell weather and some of his often colorful and picturesque language. It certainly added to a physical ability far above that which generally accompanies one of his rather small stature.

Early in World War I his clear thinking led him to recognize that it was part of a world revolution and thus that the United States should participate, and with his fearless determination always to speak for the truth, he tried to mold public opinion. Naturally, he made enemies. Late one night he was attacked by three thugs apparently hired for the job. All of them were arraigned in court, but two only after they had been discharged from the hospital. After that, his friends ceased trying to have him carry a revolver for protection.

During the next few years in France he again had to call on his physical reserves, since he went for months with only three or four hours' sleep each night. He made an enviable record in the British Expeditionary Force and, because of this, was made a Commander of the Order of St. Michael and St. George. While in England he developed a close companionship with many of the surgeons at "Barts," a relation that persisted for the rest of his life.

At Ann Arbor, free from the tension of competitive practice, he devoted his full time to teaching and to the development of the medical school and hospital. He gathered around him a group of medical men, specialists in their respective fields, who, under his stimulating leadership, proceeded to build up what is today one of the great medical schools of this country. Here also his clear thinking carried him ahead of his contemporaries. Among other things, his insistence on full-time teachers and a large hospital for clinical facilities aroused opposition. Had he been a good politician during these years, being willing to give here or there, to compromise occasionally or at times even to refrain from speaking the obvious truth, he might well have finished his work at Ann Arbor. That, however, was not his way: he must say what he believed, often to stimulate discussion and to start thinking. This was understood by his friends, but often it only served to arouse more opposition among those not accustomed to his ways. The latter did not realize that he was always willing to change his mind when shown that he was wrong, but he *must* be shown. So it was that he finally had to leave Ann Arbor.

For years he and Will Mayo had been friends, and he was at once invited to become a part of the Mayo Clinic. There, as professor of surgery, he continued his teaching, but only to graduate students. Always an inspiring teacher, he developed the seminar method to a high level. These seminars became famous throughout the country, and the exchange of ideas between students and faculty were valuable to both. No one who attended one of these sessions will forget the way in which he directed and co-ordinated the fullest discussion toward a definite end.

He had long been interested in the social and economic aspects of medicine, and during this period he began writing and speaking on this subject, which he continued to do the rest of his life. His first book, *The Doctor's Bill*, was published in 1936, and *The Patient's Dilemma* in 1940. His knowledge on the subject was extensive, and when he developed the beliefs that the evils of the present method of practice were harmful to both physician and patient and that they could be corrected to the advantage of both, he became a crusader for what he believed was the truth.

In 1939, in attempting to make a practical application of his ideas, he was one of the founders of the White Cross in Boston, a scheme for the complete prepayment of medical services. This aroused opposition among physicians but was slowly progressing when the war brought it to an end.

During his last few years, physical limitations did not prevent an active interest in current events in medicine and world affairs. He continued to lecture and to write, and his correspondence with persons in this country and England was extensive. His clear thinking and vigorously expressed opinions were unabated. His scorn of selfishness, of smallness and of low behavior in high places was not one whit diminished. His devotion to truth as he saw it was as strong as ever. His belief in a God of Law was with him always.

A great host of those who owe much to his stimulating teaching will mourn a great leader. Many of his contemporaries will miss a loyal friend. Those who loved him know that "Valiant-for-Truth" has passed over.

E. L. Y.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

GORAY — James P. Goray, M.D., of Fitchburg, died November 12. He was in his seventy-ninth year.

Dr. Goray received his degree from Harvard Medical School in 1891. He was a fellow of the American Medical Association.

MORRISON — William H. Morrison, M.D., of Springfield, died November 22. He was in his sixty-sixth year.

Dr. Morrison received his degree from Baltimore Medical College in 1905.

His widow, a son, a brother and a sister survive.

VANCE — Michael E. Vance, M.D., formerly of North Attleboro, died May 5. He was in his seventy-sixth year.

Dr. Vance received his degree from New York University Medical College in 1895. He was a member of the Rhode Island Medical Society, Pawtucket Medical Association, Attleboro Doctors' Association and a fellow of the American Medical Association.

His widow survives.

WARREN — Alva H. Warren, M.D., of Malden, died November 19. He was in his seventy-second year.

Dr. Warren received his degree from Harvard Medical School in 1900. He was a member of the New England Roentgen Ray Society and the American College of Radiology.

His widow, a daughter and a grandson survive.

WOODS — Charles E. Woods, M.D., of Fitchburg, died October 12. He was in his eighty-third year.

Dr. Woods received his degree from Dartmouth Medical School, Hanover, New Hampshire, in 1890. He was a past president of the Worcester North District Medical Society, and was the Lunenburg school physician from 1906 to 1941, when he retired from practice.

His widow, a son, a daughter and four grandchildren survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1945

RÉSUMÉ

DISEASES	OCTOBER 1945	OCTOBER 1944	SEVEN-YEAR MEDIAN
Anterior poliomyelitis	136	99	21
Chancroid	1	1	*
Chicken pox	331	370	390
Diphtheria	17	19	18
Dog bite	764	842	823
Dysentery, bacillary	39	32	32
German measles	46	35	35
Gonorrhea	657	438	416
Granuloma inguinale	0	0	*
Lymphogranuloma venereum	2	1	*
Malaria	38	36	0
Measles	648	274	373
Meningitis, meningococcal	12	20	8
Meningitis, Pfeiffer-bacillus	2	4	1
Meningitis, pneumococcal	0	2	2†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	2	0	0†
Meningitis, other forms	2	0	0†
Meningitis, undetermined	3	2	4†
Mumps	326	350	204
Pneumonia, lobar	96	159	192
Salmonella infections	5	15	6
Scarlet fever	372	456	458
Syphilis	436	408	408
Tuberculosis, pulmonary	263	230	232
Tuberculosis, other forms	23	16	29
Typhoid fever	3	1	4
Undulant fever	7	2	4
Whooping cough	638	286	375

*Made reportable December, 1943.

†Four-year average.

COMMENT

Anterior poliomyelitis cases declined during October, which is similar to the seasonal fluctuation which has been observed in previous years. There were 136 cases reported for the month, as compared with 163 during September. A further and more marked decrease can be expected in the ensuing months.

Whooping cough was more than twice as prevalent during October as it was during the same month last year and exceeded the seven-year median for October by 70 per cent.

Measles cases also markedly exceeded those reported during October, 1944, being a little less than twice as high as the seven-year median.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Actinomycosis was reported from: West Springfield, 1; total, 1.

Anterior poliomyelitis was reported from: Belmont, 1; Beverly, 1; Billerica, 1; Boston, 22; Brockton, 2; Brookline, 2; Cambridge, 2; Chelsea, 3; Clinton, 1; Colrain, 2; Dalton, 4; Danvers, 1; Dartmouth, 1; Dedham, 1; Everett, 5; Fall River, 1; Fitchburg, 1; Framingham, 1; Grafton, 1; Haverhill, 1; Hingham, 2; Hopkinton, 1; Lanesboro, 1; Lancaster, 1; Lawrence, 2; Lenox, 1; Leominster, 1; Lexington, 1; Lowell, 2; Lynn, 1; Malden, 3; Medford, 11; Milford, 1; Millbury, 1; Milton, 4; Newton, 8; North Andover, 1; Northampton, 1; Norwood, 1; Orleans, 2; Pittsfield, 2; Quincy, 6; Reading, 4; Rochester, 1; Rockland, 2; Saugus, 2; Sharon, 1; Somerville, 3; Sutton, 1; Taunton, 1; Tisbury, 1; Walpole, 1; Waltham, 1; Watertown, 1; Wellesley, 2; Whitman, 1; Winthrop, 1; Woburn, 1; Worcester, 2; total, 136.

Diphtheria was reported from: Boston, 2; Chicopee, 1; Cushing General Hospital, 1; Easton, 1; Gloucester, 5; Lynn, 1; Springfield, 3; Taunton, 1; West Springfield, 1; Worcester, 1; total, 17.

Dysentery, amebic, was reported from: Camp Edwards, 2; total, 2.

Dysentery, bacillary, was reported from: Boston, 1; Cambridge, 3; Foxboro (State Hospital), 1; Lowell, 1; Malden, 1; Newton, 1; Peabody, 2; Worcester (State Hospital), 29; total, 39.

Encephalitis, infectious, was reported from: Barre, 1; Pittsfield, 2; total, 3.

Hookworm was reported from: Camp Edwards, 3; total, 3.

Malaria was reported from: Boston, 6; Brookline, 1; Cambridge, 2; Camp Edwards, 13; Holbrook, 1; Medford, 1; New Bedford, 1; Newton, 1; Northboro, 1; Peabody, 1; Quincy, 1; Raynham, 1; Swampscott, 1; Waltham Regional Hospital, 4; Winchester, 1; Worcester, 2; total, 38.

Meningitis, meningococcal, was reported from: Boston, 2; Camp Myles Standish, 1; Framingham, 1; Hanover, 1; Lowell, 1; Malden, 2; Quincy, 1; Springfield, 1; Westboro, 1; Wilbraham, 1; total, 12.

Meningitis, Pfeiffer-bacillus, was reported from: Huntington, 1; Somerville, 1; total, 2.

Meningitis, streptococcal, was reported from: Randolph, 1; Winthrop, 1; total, 2.

Meningitis, other forms, was reported from: Boston, 1; New Bedford, 1; total, 2.

Meningitis, undetermined, was reported from: Cambridge, 1; Somerville, 1; Springfield, 1; total, 3.

Salmonella infections were reported from: Boston, 1; Cambridge, 1; Dedham, 1; Ludlow, 1; Malden, 1; total, 5.

Septic sore throat was reported from: Amesbury, 1; Attleboro, 2; Boston, 7; Camp Edwards, 1; Greenfield, 1; Merrimac, 1; Worcester, 1; total, 14.

Typhoid fever was reported from: Attleboro, 1; Boston, 1; Salem, 1; total, 3.

Undulant fever was reported from: Camp Edwards, 1; Hardwick, 1; Northampton, 1; Uxbridge, 1; Westboro, 1; Williamstown, 1; Worcester, 1; total, 7.

CORRESPONDENCE

VALUE OF BLOOD AND ITS DERIVATIVES IN CIVILIAN HOSPITALS

To the Editor: I have read the editorial on blood and blood derivatives in the October 4 issue of the *Journal* and should like to express my approval of any plan which makes easily available the use of blood in the hospitals of the Commonwealth for the good of the people. Experience in every theater of war during the last three years has built up an imposing weight of evidence that whole blood is an essential factor in the restoration of those who have lost blood to a satisfactory and safe condition. It is generally accepted that plasma alone is not an adequate substitute for whole blood when the problem is one of blood loss and a replacement of blood volume. Any mechanism which can be brought forward to continue the flow of donors to hospitals and centers

for the procurement of whole blood would greatly benefit the people of the Commonwealth.

During my military mission to Moscow in 1943 I was greatly impressed by the fact that our Russian colleagues had settled the value of blood banks for their people years before the recent war began. We in our country, who should consider ourselves as enlightened in medical matters as the Soviet peoples, must not now neglect the responsibility to see that all citizens have blood available in our hospitals when the occasion for its use arises.

ELLIOTT C. CUTLER
BRIGADIER GENERAL, M.C., A.U.S.

BOOK REVIEWS

The Story of a Country Medical College: A history of the clinical school of medicine and the Vermont Medical College, Woodstock, Vermont, 1827-1856. By Frederick C. Waite, A.M., Ph.D. 8°, cloth, 213 pp., with 8 illustrations and frontispiece. Montpelier: Vermont Historical Society, 1945. $4.50.

This is the story of the medical college at Woodstock, Vermont — a proprietary school founded in 1826 by Dr. Joseph A. Gallup of Stonington, Connecticut, which lived busily until it passed into desuetude in 1862.

Dr. Waite has done an immense amount of research in the book's creation. He describes medical education in the United States before 1826, traces the antecedents of the Woodstock school, gives a delightful description of Dr. Gallup and of how he happened to establish a medical school and, finally, tells how schools like this one became outmoded as cities grew, as means of communication advanced and, above all, as the belief became established that clinical teaching at the bedside is an essential part of medical education.

The Woodstock school filled a useful purpose in supplying doctors to its part of the world when they were badly needed. It started unpretentiously in the Eagle Hotel facing the Woodstock Common but presently moved westward into "a commodious brick building in a very eligible situation" on the edge of the village; it was twice married — to speak euphemistically — once to the Waterville College, of Maine, and once to Middlebury College, of Vermont. Neither union was felicitous, however, and so the school ended its days as independently as they were begun.

Besides writing a lively account of an interesting episode in the history of medical education, Dr. Waite has accomplished an exceptionally difficult task. He gives a complete record of everyone who had anything to do with the school — students, trustees and faculty, including a number of famous peripatetic professors; who they were, whence they came, and where and when they died. To collect authentic information of this character, obtained only with difficulty, represents particularly time-consuming and arduous effort.

The book is bound to appeal to all readers who enjoy learning of New England ways.

Cinchona in Java: The story of quinine. By Norman Taylor. With an introduction by Pieter Honig. 8°, cloth, 87 pp., illustrated. New York: Greenberg, Publishers, 1945. $2.50.

Mr. Taylor is director of the Cinchona Products Institute in New York City. He has written an interesting popular account of the discovery of cinchona and its commercial development, particularly in Java, where the bulk of quinine used by the world is produced.

The natural habitat of the genus is along the Andes in South America, from Bolivia to Colombia, and the best wildbark comes from Bolivia, but the production from this territory does not equal the local demand. When it became evident that the South American bark production could not supply the world demand, the Dutch and English, as early as 1852, in the Netherlands Indies and in India, began attempts to cultivate cinchona trees.

The Java industry began in December, 1865, with the purchase of one pound of Ledger seed gathered in Bolivia. This species is now known botanically as *Cinchona legeriana*, and most of the commercial plantations in Java today consist of Ledger grafts on *C. succiruba* stocks. *C. ledgeriana*, although high in quinine, is low in the other alkaloids; whereas, *C. succiruba*, low in quinine, is high in quinidine, cinchonine and cinchondine. Plantations of the two species in Java now supply practically all quinine and cinchona alkaloids.

C. ledgeriana is difficult to grow, but *C. succirubra* is easily cultivated. Horticulturally, the problem was solved by grafting cions of *C. ledgeriana* on stocks of *C. succiruba*; the resulting trees supply the present world demand for quinine. Proper growth requires certain climatic conditions, and the trees do best at elevations ranging between three and seven thousand feet. The hills and mountains of Java furnish ideal situations. The real harvest from a plantation does not come until the trees are fifteen to eighteen years old; at that time they have reached full vigor and the bark is thick enough to cut profitably, the quinine content being at its peak. The plantation is then destroyed. The growers must keep a constant succession of planting from seed every year to ensure an adequate supply of quinine for the world.

The book is interesting and well written and should be in all libraries, public and medical.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Manual of Tropical Medicine. Prepared under the auspices of the Division of Medical Sciences, National Research Council. 8°, cloth, 727 pp., with 284 illustrations. Philadelphia: W. B. Saunders Company, 1945. $6.00.

In this new book the contributors have endeavored to write a concise statement of the most recent available and authoritative information concerning the more important tropical diseases. Particular attention has been devoted to the epidemiology and the control of the communicable diseases of the tropics, and the most recent information concerning the therapy of these diseases has been incorporated in the text. The book is designed for use in the field, as well as in laboratories and schools and should serve as a convenient summary for public-health workers, epidemiologists and parasitologists. Some of the information on the incidence and transmission of disease in the tropics is original and hitherto unpublished. Considerable space has been devoted to medical entomology, and the illustrations in this section are morphologically accurate and should prove useful in the identification of parasites. This book should be in all medical libraries and in the libraries of physicians who come into contact with tropical diseases. It is issued as one of the series of military medical manuals sponsored by the National Research Council.

Clinical Roentgenology of the Digestive Tract. By Maurice Feldman, M.D., assistant professor of gastroenterology, University of Maryland, assistant in gastroenterology, Mercy Hospital, and consulting roentgenologist, Sinai Hospital, Baltimore. Second edition. 8°, cloth, 769 pp., with 551 illustrations. Baltimore: Williams and Wilkins Company, 1945. $7.00.

In this second edition of a special treatise, first published in 1938, the author has made the necessary changes to bring the material up to date. The book has been revised, rewritten and shortened to eliminate all unessential data, and many chapters and illustrations have been added.

Neuro-Ophthalmology. By Donald J. Lyle, M.D., lecturer on neuro-ophthalmology, Department of Anatomy, Medical College of the University of Cincinnati, and attending ophthalmologist to the Good Samaritan Hospital, Christ Hospital, Jewish Hospital, St. Mary's Hospital and Children's Hospital. 4°, cloth, 395 pp., with 234 illustrations. Springfield, Illinois: Charles C Thomas, 1945. $10.50.

The plan of this book is to bring together in a brief, comprehensive and co-ordinated manner, those many phases of

neurology in so far as they concern, directly or indirectly, neuro-ophthalmology. The book is well illustrated, and an extensive bibliography is appended to the text.

Microbial Antagonisms and Antibiotic Substances. By Selman A. Waksman, B.S., M.S., Ph.D., professor of microbiology, Rutgers University, and microbiologist, New Jersey Agricultural Experiment Station. 8°, cloth, 350 pp., with frontispiece. New York: The Commonwealth Fund, 1945. $3.75.

This special monograph discusses the broad interrelations among micro-organisms living in association, either in simple mixed cultures or in complex natural populations, with special attention to the antagonistic effects. Emphasis is laid on the significance of these associations in natural processes and on their relation to disease production in man and in domesticated plants and animals. The chemical nature of the active antibiotic substances produced by various anatagonists is described, and the nature of the antagonistic action, as well as its utilization for the practical use of disease control, is discussed. An extensive bibliography will be found at the end of the volume. This volume is recommended as a reference text for medical libraries and meets the previous high standard of Commonwealth Fund publications.

Medical Gynecology. By James C. Janney, M.D., assistant professor of gynecology, Boston University School of Medicine. 8°, cloth, 389 pp., with 97 illustrations. Philadelphia: W. B. Saunders Company, 1945. $5.00.

The scope of this book is limited to office gynecology and it has two aims: to aid the medical student in correlating didactic lectures with the experience obtained in the gynecologic clinic and to provide refresher material for the practitioner. The work is based largely on the author's experience in the clinical teaching of gynecology, and the general outline is the same as the course he gives in which he approaches the subject from the direction of the patient's complaints. Under the heading of sociomedical problems in gynecology will be found a chapter on marital maladjustments.

The Control of Communicable Diseases: An official report of the American Public Health Association. Sixth edition. 12°, paper, 149 pp. New York: American Public Health Association, 1945. 35 cents.

In 1917 a committee of the Health Officers' Section of the American Public Health Association first issued this small manual on standard regulations for the administrative control of the communicable diseases for which notification is usually required by state and municipal health authorities throughout the United States. This new edition has been revised and officially approved by the American Public Health Association and is official with the United States Public Health Service and the United States Navy, and has been approved in principle by the Surgeon General of the United States Army. The various diseases are arranged alphabetically and each disease is briefly described regarding its clinical and laboratory recognition, the etiologic agent, the source of infection, the mode of transmission, the incubation period, the period of communicability, susceptibility and immunity and the prevalence of the disease. Following this, methods of control affecting both the individual and the general population are described. Inasmuch as the legal phraseology necessary for formal regulations differ in each state, such regulations are not included in the text. This manual should prove useful to all physicians coming in contact with communicable diseases.

NOTICES

ANNOUNCEMENTS

Dr. Archie A. Abrams has resumed the practice of gynecology and obstetrics at 475 Commonwealth Avenue, Boston.

Dr. Marshall K. Bartlett, having returned from military service, is resuming the practice of surgery at 264 Beacon Street, Boston.

Dr. Theodore B. Bayles, having returned from service with the United States Army, announces the reopening of his office at 372 Marlborough Street, Boston, for the practice of internal medicine.

Dr. Emmanuel Deutsch is resuming his practice at 469 Beacon Street, Boston.

Dr. Sydney Ellis has resumed his practice of obstetrics and gynecology at 311 Commonwealth Avenue, Boston.

Dr. James Andre Lamphier, having returned to civilian practice, announces the opening of his office in the Professional Building, 270 Commonwealth Avenue, Boston, for the practice of obstetrics and gynecology.

Dr. Samuel S. Levinson, having returned from active service with the United States Army, has resumed the practice of general surgery at 483 Beacon Street, Boston.

Dr. Julius Loman announces the removal of his office to 483 Beacon Street, Boston.

Dr. Charles L. Short announces the reopening of his office at 264 Beacon Street, Boston, for the practice of internal medicine, with a particular interest in arthritis.

Dr. John W. Strieder announces that Dr. Joseph P. Lynch will be associated with him in the practice of thoracic surgery at 171 Bay State Road, Boston.

Dr. Fred F. Weiner is resuming the practice of urology at 231 Main Street, Brockton.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, December 18, at twelve noon. Dr. Theodore L. Badger will speak on the subject "Medical Perambulations through Ireland, England and France." Dr. A. J. Cregg will preside.

Physicians are cordially invited to attend.

VAN METER PRIZE AWARD

The American Association for the Study of Goiter again offers the Van Meter Prize Award of three hundred dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. Provided essays of sufficient merit are presented in competition, the award will be made at the annual meeting of the association, which will be held in Chicago in April or May, 1946.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length and must be presented in English; a typewritten double-spaced copy should be sent to the corresponding secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia, not later than February 20, 1946. The committee that will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the *Proceedings* of the association. This will not prevent its further publication, however, in any journal selected by the author.

(*Notices continued on page xvii*)

NOTICES (*Continued from page 710*)

MISSISSIPPI VALLEY MEDICAL SOCIETY 1946 ESSAY CONTEST

The Mississippi Valley Medical Society is resuming its annual essay contest, which has not been held during the war. In 1946 it offers a cash prize of $100, a gold medal and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society to be held at St. Louis, on September 25, 26 and 27; the society reserves the exclusive right to publish the essay in its official publication, the *Mississippi Valley Medical Journal*. All contributions shall not exceed 5000 words, shall be typewritten in English in manuscript form, shall be submitted in five copies and must be received not later than May 1, 1946. Further details may be secured from Harold Swanberg, M.D., Secretary, Mississippi Valley Medical Society, 209-224 W. C. U. Building, Quincy, Illinois.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, December 13

Friday, December 14

*9:00-10:00 a.m. Some Clinical Considerations of Louse-Borne Typhus. Lt. Comdr. Andrew Yeomans. Joseph H. Pratt Diagnostic Hospital.
*9:00-10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.
*10:00 a.m.-12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.
10:50 a.m. Papular Eruptions of the Skin. Dr. E. A. LaFreniere. (Postgraduate clinic in dermatology and syphilology.) Amphitheater, Dowling Building. Boston City Hospital.
12:00 m.-1:00 p.m. Clinicopathological conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

Monday, December 17

*12:00 m.-1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

Tuesday, December 18

*9:00-10:00 a.m. Medical clinic. Infants' Hospital.
*12:00 m. South End Medical Club. Headquarters, Boston Tuberculosis Association.
*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

Wednesday, December 19

*9:00-10:00 a.m. Slipping Epiphysis of the Head of the Femur in Growing Children. Dr. Russell Sullivan. Joseph H. Pratt Diagnostic Hospital.
*12:00 m. Clinicopathological conference. Children's Hospital.
*12:00 m.-1:00 p.m. Clinicopathological conference. Cambridge Hospital.

*Open to the medical profession.

October 1-December 10, 1945 and January 7-April 22, 1946. Metropolitan State Hospital. Eleventh postgraduate seminar in neurology and psychiatry. Page 314, issue of September 6.

December 11. Harvard Medical Society. Peter Bent Brigham Hospital. 8 p.m.

December 11. Greater Boston Medical Society. Page 672, issue of November 29.

December 12. Legislative conference. Page 638, issue of November 22.

December 12. New England Dermatological Society. Page 638, issue of November 22.

December 12. New England Obstetrical and Gynecological Society. Page 638, issue of November 22.

December 13. The Treatment of Venous Thrombosis. Dr. Robert R. Linton. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

December 18. South End Medical Club. Page 710.

February 2. American Board of Obstetrics and Gynecology. Page 514, issue of October 25.

District Medical Society

WORCESTER

December 12. Worcester City Hospital.
January 9. St. Vincent Hospital.
February 13. Worcester State Hospital.
March 13. Worcester Memorial Hospital.
April 10. Hahnemann Hospital.
May 8. Annual meeting.

Harvard Medical School

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(In War and in Peace)

42 PRIZES

21 OF THE 42 PRIZES ARE RESERVED FOR MEDICAL OFFICERS OF THE ARMED FORCES. THE OTHER 21 PRIZES ARE FOR CIVILIAN PHYSICIANS

The American Physicians Art Association, through the cooperation of Mead Johnson & Company, announces the following Prize Contest:

1. **SUBJECT:** "Courage and Devotion Beyond the Call of Duty" — on the part of members of the medical profession — in military or civilian practice. Any contestant may portray either the military or civilian aspect of the subject (or both, if shown in one piece).

2. **MEDIA:** The physician-artist's choice of one of the following:

   a. PAINTING in oil or egg tempera.
   b. WATER COLOR, transparent or opaque.
   c. SCULPTURE in any medium.
   d. DRAWING in any medium.
   e. PRINTS, including etching, engraving, lithography, wood block and linoleum block (on paper or cloth).
   f. PHOTOGRAPHY, including bromoil, tinted and Kodachrome, as well as photo-montage.

   SUGGESTIONS: COMPLETE SKETCHES FOR MURAL DECORATIONS: In oil, egg tempera or water color drawing; PHOTO MURAL; BAS RELIEF SCULPTURE: are all eligible.

3. **ELIGIBILITY — See Footnote ★**

4. **DEFINITION — See Footnote ★**

5. **PRIZES: Forty-two prizes, divided amongst the two groups of physicians:**

To medical officers:	To civilian physicians:
1 $2,000 War Bond (E or F series)	1 $2,000 War Bond (E or F series)
10 $1,000 War Bonds (E or F series)	10 $1,000 War Bonds (E or F series)
10 $ 500 War Bonds (E or F series)	10 $ 500 War Bonds (E or F series)

No physician may submit more than one piece nor win more than one of the 42 prizes. No physician is eligible for a prize unless he also submits for exhibition at either the 1945 or the 1946 annual exhibition of the A.P.A.A. at least one other original work (not previously exhibited at an A.P.A.A. Exhibition) in any medium, on any subject of his own choice. Prizes will be awarded on a basis of conception and execution, irrespective of medium employed.

6. **JUDGES — See Footnote ★**

7. **EXPIRATION DATE — See Footnote ★**

8. **PURPOSE OF THE COMPETITION:** To memorialize the heroism and devotion of the medical profession in war and peace. All exhibitors (including prize-winners) shall retain ownership of their pieces. It is understood, however, that the A.P.A.A. shall have reproduction rights and also the privilege, for a period of three years after the close of the contest, of displaying prize-winning objects, at art museums, libraries, county medical societies, medical schools, hospitals, and similar institutions for the purpose of enhancing the public's estimate of the medical profession. The Association shall also have the right to offer institutions such as those mentioned above, the privilege of copying any of the prize-winning objects for use as murals, cornerstones, friezes, architectural designs, etc. — for the purpose of memorializing the medical profession's importance in war and in peace.

★ **FURTHER INFORMATION** available on request of the Association's Secretary, Dr. F. H. Redewill, Flood Bldg., San Francisco, Cal., or Mead Johnson & Co., Evansville 21, Ind., U.S.A.